THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

SEPTEMBER 15, 1959 • VOL. 81, NO. 6

POLIOVIRUS ANTIBODY RESPONSE AFTER VARIOUS VACCINATION SCHEDULES AND AT DIFFERENT AGES*

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A PREVIOUS REPORT[1] described the antibody response to poliomyelitis vaccine in three groups of schoolchildren, one given initial vaccination in the spring of 1955 and two vaccinated in 1956. This report contains further observations on these groups as well as the results of vaccination of infants and adults, and of schoolchildren who received a primary vaccination of one dose only. The data given in the first study are included in this report.

Certain questions are being asked concerning the spacing of doses, the duration of antibody, and the response in infants. These problems are discussed on the basis of the results presented, and of the observations of others, particularly where the latter are more detailed or extensive.

GROUPS OBSERVED

1. Children 8 to 9 years of age¶ (third grade schoolchildren) in East York-Leaside, Toronto, given initial vaccination in 1955 (S series).

2. Children 6 to 7 years of age (first-grade schoolchildren in East York-Leaside, Toronto, given initial vaccination in 1956 (Y_1 series).

3. Children 13 to 14 years of age (eighth-grade schoolchildren) in East York-Leaside, Toronto, given initial vaccination in 1956 (Y_2 series).

4. Infants 3 to 12 months of age, of whom approximately one-third were under the care of Dr. C. S. Anglin, Toronto, Ontario, and the remainder were in attendance at health clinics in Hamilton, Ontario, given initial vaccination in 1956 (K_2 series).

5. Children 6 to 14 years of age in Alberta and British Columbia, who had received a single inoculation only as primary vaccination in 1956, with a second dose as the booster or recall dose after either seven or ten months. Blood samples were available before and after the booster dose only.

6. Adults 21 to 60 years of age, members of the staff and employees of the Connaught Medical Research Laboratories, Toronto, vaccinated between 1955 and 1957. They were born in Canada and resident in Ontario most of their lives.

METHODS

With the exception of the groups in the two western provinces, as noted above, blood samples were taken immediately before the first dose of vaccine and two weeks after the last dose of the initial course of inoculation. This consisted of two doses given subcutaneously four weeks apart, except in one portion of the 8- to 9-year-old group in which three doses were given with an interval of one week between the first and second doses, and three weeks between the second and third inoculations. It was shown in the previous report that there was no appreciable difference between the response to two doses and the response to three doses given at these particular intervals; hence the two parts of this age group are not shown separately except where a further comparison of varying numbers of doses is made.

The interval between the last injection of the initial course and the booster dose was approximately ten months, except in one of the western groups in which it was seven months. Blood samples were taken immediately before and two weeks after the booster dose. In the first group vaccinated—the 8- to 9-year-old children—a fifth blood sample was taken 18 months after the booster dose.

Antibody level was estimated by the modified metabolic inhibition test described by Salk, Youngner and Ward,[2] as outlined in the previous report by Armstrong, Moss and Potter.[1] Samples taken before and after the initial course of inoculation were tested together, as were samples

*From the Connaught Medical Research Laboratories, Toronto. Presented in part at: the Forty-ninth Annual Meeting of the Canadian Public Health Association, Vancouver, British Columbia, May 20, 1958; the Thirty-fifth Annual Meeting of the Canadian Pædiatric Society, St. Andrews-by-the-Sea, New Brunswick, June 13, 1958; the Twenty-sixth Annual Meeting of the Laboratory Section, Canadian Public Health Association, Montreal, Quebec, December 16, 1958.

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¶Age at time of initial vaccination.

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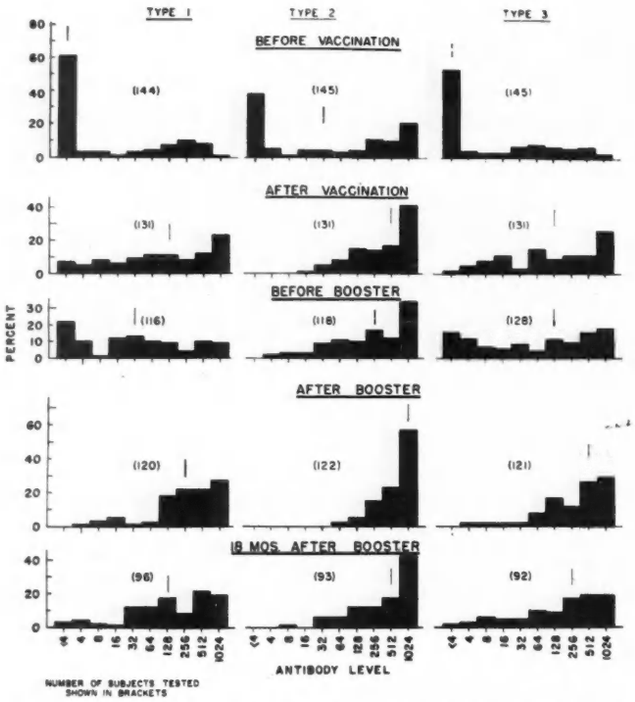

Fig. 1.—Percentage distribution of poliovirus antibody levels: children 8 to 9 years of age (S series).

taken before and after the booster dose, with suitable controls for the sensitivity of the test.

Changes in Antibody Levels After Vaccination

The percentage distribution of antibody levels at successive stages in the various groups is shown in Figs. 1 to 5. The median level is shown as a short vertical line on each diagram. This value was used since the geometric mean cannot be calculated unless finite values be assigned to each of the individual antibody levels. This cannot

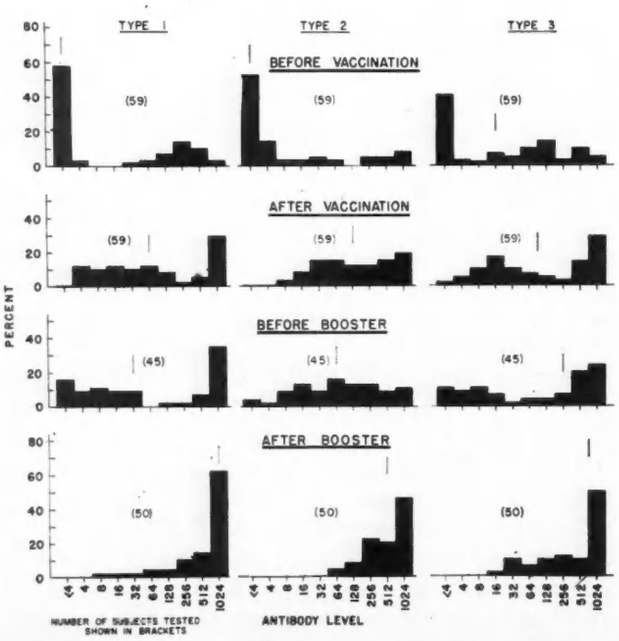

Fig. 2.—Percentage distribution of poliovirus antibody levels: children 6 to 7 years of age (Y1 series).

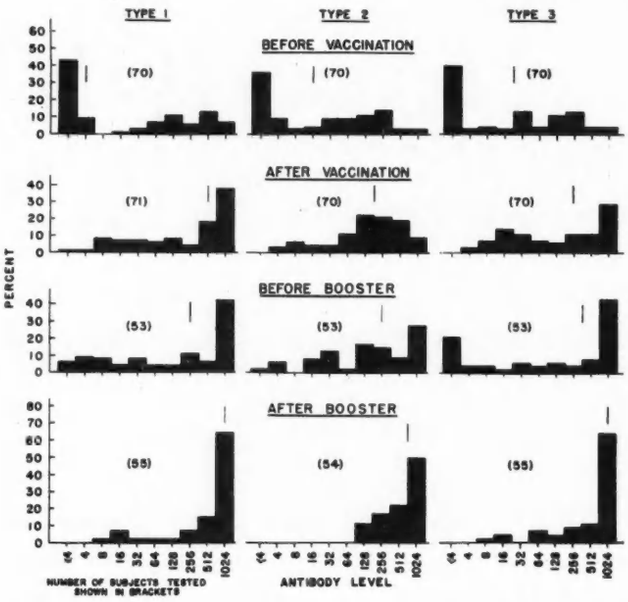

Fig. 3.—Percentage distribution of poliovirus antibody levels: children 13 to 14 years of age (Y2 series).

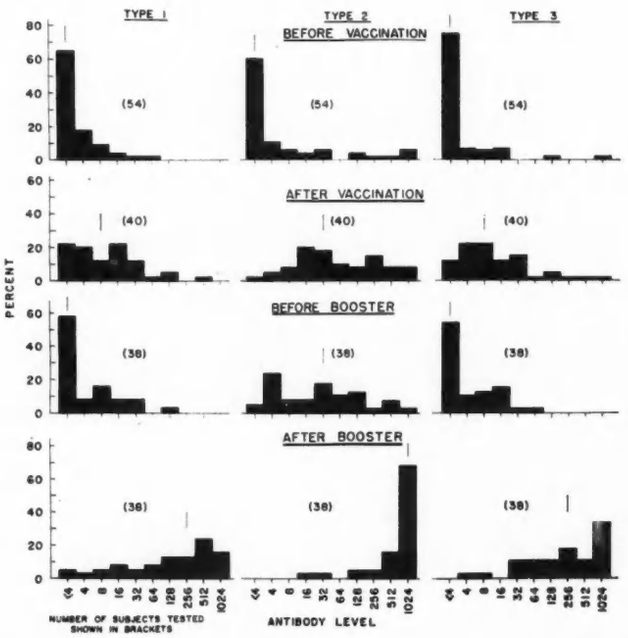

Fig. 4.—Percentage distribution of poliovirus antibody levels: infants 3 to 12 months of age (K2 series).

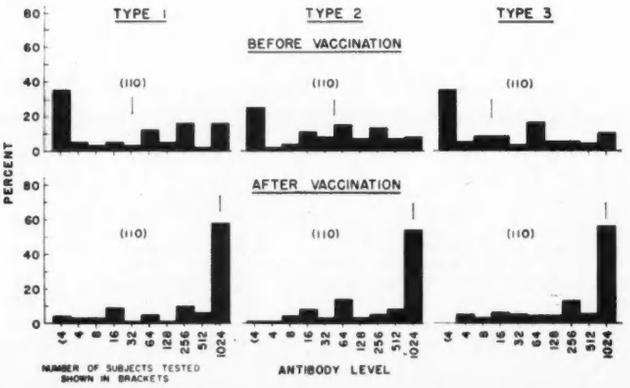

Fig. 5.—Percentage distribution of poliovirus antibody levels: adults 21 to 60 years of age (F series).

TABLE I.—RESPONSE IN INDIVIDUALS WITHOUT ANTIBODY BEFORE VACCINATION—THE "TRIPLE-NEGATIVES"

Age group	*Sample tested*	*Number of subjects*	*Subjects with antibody* Type 1 No.	%	Type 2 No.	%	Type 3 No.	%
Infants <1 Year	After vaccination	19	13	68	19	100	16	84
	Before booster	14	2	14	13	93	3	21
	After booster	14	13	93	14	100	14	100
Children 6-14 years	After vaccination	38	31	82	38	100	34	89
	Before booster	32	13	41	29	91	15	47
	After booster	34	34	100	34	100	34	100
Adults	After vaccination	15	13	87	14	93	15	100

properly be done if a proportion of the values falls outside the range of levels actually measured, i.e. where the titration is carried out to a limited dilution only (in these tests, 1:1024), or where some sera are negative at the lowest dilution tested (1:4). Though useful comparisons can be made, the accuracy is not sufficient for strict comparisons of averages.

The distribution of antibody levels after natural infection is seen in the pattern of the pre-vaccination samples of children and adults. For any one type, approximately half of the children and one-third of the adults have levels below 4, i.e. are without detectable antibody at a serum dilution of 1:4. Most but not all children show a response after the initial course of vaccination, there being an occasional failure in type 1 and in type 3 responses. In the ten-month period after initial vaccination there appears to be a decline of about two-fold to four-fold in median antibody levels. This is not an accurate figure and in some groups no decline, or a rise, is seen. This is not the result of intercurrent infection, but is due to a small shift in the level of sensitivity of the test. After the booster dose there is a marked shift to higher levels, all children having developed antibody to all three types.

Some two-thirds of the infant group were without detectable antibody of any one type at the time of initial vaccination. Of the infants with antibody, five, all over five months of age, had relatively high levels of type 2 antibody which must be considered as representing active response to infection. These type 2 values have been excluded from tables relating response to presence of maternal antibody. The response in infants appears less than in children, but in spite of low levels ten months after the initial course, the infants responded fairly well to the booster dose. Two out of 38 failed to develop type 1 antibody.

MAINTENANCE OF ANTIBODY AFTER THE BOOSTER DOSE

In the group of 8- to 9-year-old children vaccinated in 1955, blood samples were taken 18 months after the booster dose. The majority still showed satisfactory levels, an occasional one only having dropped below detectable level. The loss of antibody in this period appeared to be about two-fold.

Salk[3] has shown satisfactory antibody levels one year after the booster dose in various groups of children without antibody before vaccination, and has described the maintenance of antibody up to three and one-half years in a group of 13 children. All 13 children retained measurable levels of all three types of antibody, with the exception of one child whose titre of type 1 antibody dropped below the lowest dilution tested (1:4) between two and one-half and three and one-half years after the booster dose. Infection was excluded as a factor in the persistence of antibody. Brown *et al.*[4] determined serum antibody levels in children and infants two years after the booster dose and found the average loss to be three-fold to four-fold. He noted that the rate of antibody decline was similar to that reported by Lennette in patients convalescent from paralytic disease which had been confirmed by virus isolation.

Comparisons with another type of antigen such as diphtheria toxoid cannot readily be made, but it is of interest to note that allowance for a five-fold drop in antitoxin level in four years was recommended by Fraser.[5] The duration of measurable antibody appears to be directly related to the level attained after vaccination. As this varies greatly from one individual to another, it is well to bear in mind that the persistence of antibody varies also. There seems to be no evidence as yet that maintenance of immunity by means of Salk-type vaccine will present any problems very different from those presented by other antigens.

RESPONSE IN "TRIPLE-NEGATIVES"

The response of individuals initially without antibody of any of the three types—the "triple-negatives"—is shown in Table I. These results give the clearest picture of the effect of vaccination. The numbers are small, particularly the number of adults, but the responses of these subjects in the different age groups are consistent with the patterns of response of the groups as a whole. Though 82% only of children of school age produced type 1 antibody after the initial course of vaccination, and of these, antibody titres fell below detectable level in about one-half within ten months, all developed antibody to all three types after the booster dose. One of 14 infants and two of 15 adults failed to respond to type 1 antigen; one adult did not respond to type 2 antigen.

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Different Dose Schedules

The percentage of children with antibody before and after the booster dose, grouped according to the number of doses given in the initial course, is shown in Table II. There are certain obvious limitations in the comparisons shown in this table. Since, as noted above, no blood specimens were available before and after primary vaccination in the children who received one dose only at this time, those negative for type or triple-negative could not be selected. Thus comparability cannot be assured. However, since the proportions positive before the booster dose in these children were about 70% for each of the three types, the proportions were almost certainly lower than this before the initial dose, and were probably fairly similar to those in the Ontario children where the figures were between 40 and 60% before the first dose.

Salk[7] showed a very definite rise in antibody levels after a second dose given four weeks after the first dose, and observed that "the low proportion of response to the first dose was converted to a high proportion by the second". The marked difference in the response after one dose as compared with that after two doses, shown in Table II, and the type of response to two doses seen in Figs. 1 to 5 and Table I, are consistent with the latter observation by Salk. Brown, Rabson and Craig[8] found two doses eight to ten weeks apart as effective as three injections at 0, 1 and 5 weeks.

The percentage with antibody, following the second dose given after varying intervals, is shown in Table III. The results are similar with intervals of one, seven or ten months. Though no firm conclusion can be drawn since the comparability of the groups cannot be demonstrated, the similarity

TABLE II.—Varying Number of Doses in Initial Course: Children—Ages 6 to 14 Years
Percentage With Antibody Before and After Booster Dose Given 10 Months Later

No. of doses	*Percentage positive before and after booster dose*					
	Type 1		*Type 2*		*Type 3*	
	Before	*After*	*Before*	*After*	*Before*	*After*
3.....	84% (51)*	100% (57)	100% (54)	100% (54)	90% (57)	100% (58)
2.....	84% (166)	100% (172)	98% (166)	100% (173)	84% (168)	100% (176)
1**.....	67% (60)	98% (60)	70% (60)	98% (60)	68% (60)	100% (60)

* (51) = number of subjects tested.
** 30 with interval of seven months.

The results indicate no difference in type 1 antibody response between the children given three doses and those given two doses, and none of probable significance in type 2 or type 3 responses, confirming the observation in a previous report. It must be emphasized that in this three-dose schedule the second dose was given one week after the first. Since this period is before the secondary response phase, the second dose could be expected to act chiefly as an increase in the amount of the first dose. The effect of such an increase is not measurable in this type of study and is of little practical importance.

Salk[6] reported that in children without antibody before vaccination with three doses at intervals of two weeks, no further increase in mean antibody level was observed after the third dose; also, with the interval between the second and third doses increased to three weeks there was little increase after the third dose. Lack of response to a dose of vaccine four or five weeks after the first dose has not been reported elsewhere. He considered the response during the first five weeks to be of primary type, and contrasted the results with those in other children who showed a marked response to a dose given seven months after the initial course. These observations appear to have been, in part at least, the basis for his recommendation of an initial course of two doses, with the third dose as a booster dose seven months or more later. In a later report suggests that the real difference is not great. Information on this point has existed for several years. It has been shown by Salk and by Brown that the response to a delayed second dose is somewhat better than the response to a second dose given after one month. Thus, in answer to the question "If after one dose an interval of several months has elapsed, should the entire inoculation series be started again?" it can be said that it is unnecessary; inoculation may be continued as if there had been no delay.

To answer this question, Brown[9] compared the response when a five-month interval had elapsed with the response when the interval had been one month. He found the response somewhat better after the longer interval. The difference was not marked and the groups compared were different in age. An answer to this question had already been supplied in data given by Salk[10] as evidence for greater response with an increasing interval up to seven months between the second and third doses. The results he gave show a greater type 2 antibody response to a second dose when the interval was increased from one to two months, but no further increase in response on successive monthly increases up to six months; after an initial course of two doses there is shown an increase in response with each increase of a month in the interval between the second and third doses up to six months, though the differences between results at four months and longer

TABLE III.—VARYING INTERVAL BETWEEN FIRST AND SECOND DOSE (DELAYED SECOND DOSE): CHILDREN—AGES 6 TO 14 YEARS
PERCENTAGE WITH ANTIBODY BEFORE AND AFTER SECOND DOSE

Interval between doses (months)	*Percentage positive before and after second dose*					
	Type 1		*Type 2*		*Type 3*	
	Before	*After*	*Before*	*After*	*Before*	*After*
10	67% (30)*	97% (30)	80% (30)	97% (30)	73% (30)	100% (30)
7	67% (30)	100% (30)	60% (30)	100% (30)	63% (30)	100% (30)
1	— —	97% (206)	— —	100% (206)	— —	98% (206)

* (30) = number of subjects tested.

intervals appear minimal. A good response was reported by Salk[11] when the third dose was given three months after the second.

In a trial reported separately[12] infants given three doses of poliomyelitis vaccine—combined with other antigens or alone—one month apart, showed a much better response than did the infants described in this report who received two doses one month apart. After three doses, 97% of infants initially negative developed type 1 antibody, 80% still showing detectable levels a year later. After two doses the corresponding figures in infants were 74% and 37%, and in schoolchildren without pre-vaccination antibody, 82% and 41% respectively. Thus it is apparent that a third injection, given one month after the second, produced a marked increase in antibody.

From these various observations it would appear that the secondary response phase begins a little less than four weeks after the first stimulus, and continues to develop during the next month and possibly longer. The period required for full development is not established as yet, and possibly is not any fixed time but dependent on the intensity of the stimulus (potency of the antigen), the number of doses, age and other factors. There is no strong evidence against the concept that, with a total of *three* doses of vaccine of good potency, fairly full development of the response mechanism is reached as early as two months after the first dose, and any further development with lengthening of the second interval is relatively small. Increasing both intervals to six weeks might give a somewhat better response but this has not been demonstrated as yet.

In practical terms, then, it may be said that the second inoculation should be given not less than four weeks after the first dose, and the third injection not less than four weeks after the second dose but before the next poliomyelitis season. Until more is known it may be considered preferable to increase the interval between the second and third inoculations within these limits. This is essentially similar to the recommendation made by Salk[7] except for his emphasis on the longer period of seven months before the third dose. Nevertheless, he stated clearly that the third injection should be administered before the ensuing seasonal prevalence.

TABLE IV.—RESPONSE AT DIFFERENT AGES. PROPORTION RESPONDING AFTER 2 DOSES 4 WEEKS APART

Age group (years)	*Initially negative for type*		
	Type 1	*Type 2*	*Type 3*
<1	26/35 = 74%	33/33 = 100%	32/41 = 78%
6 - 14	132/142 = 93%	102/102 = 100%	117/121 = 97%
21 - 60	91/98 = 93%	80/81 = 99%	82/82 = 100%
	Initially "triple-negative"		
	Type 1	*Type 2*	*Type 3*
<1	13/19 = 68%	19/19 = 100%	16/19 = 84%
6 - 14	31/38 = 82%	38/38 = 100%	34/38 = 89%
21 - 60	13/15 = 87%	14/15 = 93%	15/15 = 100%

RESPONSE AT DIFFERENT AGES

The response in infants three to 12 months of age, children and adults, initially without antibody of specific type, also in those without poliovirus antibody of any type, is shown in Table IV. In those without antibody of specific type the responses to type 1 antigen and to type 3 antigen are both somewhat poorer in the infants than in the children. Each of these differences is highly significant (significant at the 1% level). However, infants and children in this category are also different in one important respect. Some of the children possessed active antibody against one of the other two types, or both, from previous infection. Previous infection with type 2 virus has been shown by Salk[15] to increase the response to types 1 and 3 antigens. Maternal antibody of the heterologous type, since it does not arise from previous infection of the infant, would have no such effect; therefore, infants initially negative for a specific type, whether they possess heterologous antibody or not, are essentially similar to the "triple-negative" infants. It can be seen in Table IV that they do, in fact, respond similarly. Thus, in the infants and children initially without antibody of specific type, the poorer response in infants cannot be ascribed to age. Any effect due to age,

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TABLE V.—Response in Infants at Different Months of Age

Age (months)	Proportion of infants with antibody 10 months after 2 doses 4 weeks apart: Initially negative for type — Type 1	Type 2	Type 3	Initially positive for type (Maternal antibody) — Type 1	Type 2	Type 3
3 - 5	6/10	9/9	5/9	4/9	8/9	6/10
6 - 8	3/10	10/11	3/12	1/3	—	0/1
9 - 12	1/7	6/7	3/8	1/1	—	—

if present, cannot be distinguished from the effect of heterologous sensitization of some of the children.

In the "triple-negatives" the response to type 1 antigen appears less in infants than in children: also, as seen in Table I, the proportion with type 1 or type 3 antibody ten months after the initial course is lower in infants than in children. None of these differences, taken alone, is significant. Taken together, these observations suggest that the infants did not respond quite as well as children six years of age or older, but no definite conclusion can be drawn. Such difference as occurred was small. There was no difference of any significance after the booster dose.

given in Table VI. It can be seen that, measured at ten months after the initial course, at a time when even the youngest infants were 14 or 15 months old and maternal antibody would have virtually disappeared, there was no difference. It must be noted, however, that the levels of maternal antibody in these infants were low. In infants with higher levels, to whom combined vaccine was given,[12] there was evidence of some interference by maternal antibody. This effect was reported by Perkins, Yetts and Gaisford,[13, 14] though it is difficult to estimate the extent of the effect from the results presented. The results of the infant series described in this report, and of

TABLE VI.—Response in Infants (Ages 3 to 12 Months) With and Without Maternal Antibody of Specific Type and in Children (Ages 6 to 7 Years) Without Antibody of Specific Type After 2 Doses 4 Weeks Apart

Age group (years)	Time after vaccination	Proportion of subjects with antibody and median antibody level*: Initially negative for type — Type 1	Type 2	Type 3
<1	2 weeks	26/35 = 74% (1/4-1/8)	33/33 = 100% (1/32)	32/41 = 78% (1/16)
	10 months	10/27 = 37% (<1/4-1/4)	25/27 = 93% (1/16)	11/29 = 38% (<1/4-1/4)
		Initially positive for type (maternal antibody)		
		Type 1	Type 2	Type 3
	10 months	6/13 = 46% (<1/4-1/4)	8/9 = 89% (1/4-1/8)	6/11 = 55% (1/4)
		Initially negative for type		
		Type 1	Type 2	Type 3
6-7	2 weeks	27/28 = 96% (1/16)	24/24 = 100% (1/32)	19/19 = 100% (1/16)
	10 months	19/26 = 73% (1/8)	19/21 = 90% (1/16-1/32)	12/17 = 70% (1/4-1/8)

* Median antibody shown in brackets.

Brown[16] reported that infants two to 12 months of age and children one to five years of age responded well to poliomyelitis vaccination. Though he did not conclude that the response was better in children than in infants, he observed that the children who possessed actively acquired antibodies before vaccination appeared to respond better than infants with passive antibodies. He found that infants two to six months of age responded as well as infants seven to 11 months of age. In Table V the proportion of infants developing and retaining antibody for ten months is shown for three age groups. The infants three to five months of age responded as well as the older infants. It must be noted that this study did not include infants less than three months of age, in whom the response may be poorer.

Primary Vaccination in Presence of Maternal Antibody

The response in infants with and without maternal antibody is shown in Table V. A comparison of the results in infants and in children without antibody of specific type before vaccination is

the trial of combined vaccine,[12] indicate that three doses of vaccine injected one month apart will produce a satisfactory response in most infants three months of age or older.

Summary and Conclusions

Observations on the response of children, infants and adults to poliomyelitis vaccine are presented. A high rate of response followed initial vaccination with two doses in children and adults. After the booster dose all children, including those initially without antibody of any of the three types, developed antibodies of all three types. Satisfactory levels were present in children 18 months after the booster dose. There is no evidence as yet that maintenance of antibody by Salk-type vaccine will present special problems.

When spaced four weeks or more apart, two doses gave a much greater response than one dose. The response to a second dose when given seven or ten months after the first dose was as good as when given one month after the first inoculation. Observations by others indicate that it may be better. If, therefore, there should be a delay in giving the second dose, inoculations may be continued as if there had been no interruption in the series.

When given within a period of four weeks, three doses produced no greater response than two doses; however, observations described in another report indicated a greater response after three doses when the series extended over a period of two months, with a month between doses. The observed responses are consistent with the concept that the secondary response phase begins within four weeks and develops markedly during the second month after the primary stimulus. The period required for maximum development is not yet established. It may possibly vary, depending on the potency of the antigen, the number of doses, age and other factors.

It is recommended that the second dose be given not less than four weeks after the first dose, and the third dose not less than four weeks after the second, preferably after a longer period but before the next poliomyelitis season.

Infants three to 12 months of age did not respond to vaccination as well as children, but the difference was not great. Two and probably three factors play a part in this difference, namely, sensitization from previous infection, maternal antibody and age. A higher proportion of children than infants have prior sensitization which increases the response to vaccine. Higher levels of maternal antibody decrease the response in some of the infants. Some developmental factor may also play a part, but any difference due to age, between infants three months of age or older and children, is very small. Low levels of maternal antibody do not inhibit response. Most infants three months of age or more respond satisfactorily after three doses of vaccine one month apart.

These studies were made possible by the active cooperation of the following medical officers of health and with the assistance of various members of their staffs: Dr. W. Mosley, Director, East York-Leaside Health Unit, Toronto, Ontario; Dr. L. A. Clarke, Medical Officer of Health, Hamilton, Ontario; Dr. A. Somerville, Deputy Minister of Health, Alberta; Dr. G. F. Amyot, Deputy Minister of Health, British Columbia.

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RÉSUMÉ

La réaction humorale de l'organisme au vaccin antipoliomyélitique chez les enfants et les adultes forme l'objet de cette étude. Les deux premières injections produisent une bonne réponse dans la majorité des cas. Après la dose de rappel tous les enfants, y compris ceux qui au début étaient dépourvus d'anticorps, produisent des anticorps des trois types. On a retrouvé des taux satisfaisants 18 mois après la dose de rappel de sorte qu'il n'y a aucune raison de croire que les anticorps ne puissent être conservés à un niveau utile par l'usage du vaccin genre Salk. A un intervalle de quatre semaines ou plus deux injections produisent un degré d'immunité beaucoup plus élevé qu'une seule. La réponse est aussi bonne lorsque la deuxième dose est administrée sept ou dix mois après la première au lieu d'un mois. D'aucuns prétendent qu'elle est même supérieure. Si l'administration de la deuxième dose retarde il convient donc de continuer comme s'il n'y avait eu aucune interruption dans la série.

Si les trois injections sont données dans une période d'un mois la réponse n'est pas meilleure que si seulement deux injections avaient été données. Cependant il y a une certaine augmentation de l'immunité si ces trois doses sont données en deux mois. Ces observations appuient le concept voulant que la phase secondaire de l'immunité commence dans la période de quatre semaines et s'accroisse considérablement pendant le deuxième mois après la prise de contact. On n'a pas encore déterminé la période ou se produit le développement maximum. Elle peut dépendre de l'activité de l'antigène, du nombre d'injections, de l'âge et d'autres facteurs. On recommande que la deuxième injection soit donnée dans un délai de pas moins de quatre semaines après la première, et la troisième, pas moins de quatre semaines après la seconde, et de préférence après un période plus longue mais cependant avant la prochaine saison de poliomyélite.

Les nourrissons de trois à douze mois n'ont pas obtenu un degré d'immunité aussi élevé que celui des enfants mais la différence n'est pas grande. Deux et probablement même trois facteurs entrent en jeu dans l'établissement de cette différence, à savoir: la sensibilisation par les infections antérieures, la présence d'anticorps maternels et l'âge des sujets. Une plus grande proportion d'enfants que de nourrissons possèdent une sensibilisation antérieure qui augmente la réponse au vaccin. Un titre élevé d'anticorps maternels diminue la réaction de certains nourrissons. Certains facteurs de croissance peuvent aussi contribuer mais la différence qui dépend de l'âge entre les nourrissons de trois mois ou plus et les enfants est très petite. Les anticorps maternels de bas titre ne s'interposent pas. La plupart des enfants âgés de trois mois ou plus obtiennent un degré d'immunité satisfaisant après trois injections espacées d'un mois chacune.

IS THE TAIL WAGGING THE DOG?

"The tremendous emphasis placed on research in every branch of endeavour is nowhere more enthusiastically advocated than in our medical schools. It should be understood at once that research in medicine has brought most of the amazing progress which has been made in the past 50 years. This half century has probably seen developments more important than the total of the several preceding centuries. The same applies to industry.

"It is, therefore, quite natural and human to feel that research can accomplish anything when enough money is provided. Enormous amounts have been allocated by various federal agencies, drug manufacturers, foundations and philanthropists. It is not surprising, therefore, that research has risen to such heights as to obscure the clinical teaching in some of our schools. Indeed in many of our medical societies the amount of research done and the *number* of papers published are considered more important as requisites for membership than the clinical ability of the applicant.

"When a new professor is considered for a clinical department in our medical schools his research accomplishments are thought more important than his clinical ability and experience.

"The duplication of effort is out of all reason. The federal agencies make grants for the same studies in many parts of the country, the organizations interested in special diseases collect large amounts for research along specialized lines and when their projects are accomplished some spread into other fields already covered."—C. Williams: *Virginia M. Month.*, 86, 305, 1959.

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Sept. 15, 1959, vol. 81

DIPHTHERIA AND TETANUS TOXOIDS COMBINED WITH PERTUSSIS AND POLIOMYELITIS VACCINES*
CLINICAL TRIAL OF A QUADRUPLE ANTIGEN

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SHORTLY after the introduction of poliomyelitis vaccine for general use in children in 1955, consideration was given to the addition of this new antigen to the already widely accepted multiple antigen Diphtheria Toxoid, Pertussis Vaccine and Tetanus Toxoid (combined), or DPT. The first point for investigation was the stability of poliomyelitis vaccine in the presence of the other components of the mixture and the selection of a suitable preservative for the preparation as a whole. The second point for investigation was the response of infants under one year, and in particular under six months, to the poliomyelitis vaccine component, since the first dose of DPT is usually administered between three and six months of age in order to induce an early active immunity to whooping cough.

TABLE I.—COMPARISON OF POTENCIES OF POLIOMYELITIS VACCINES AND DPT POLIO VACCINES CONTAINING CORRESPONDING LOT, AVERAGE OF 10 LOTS

	*Geometric mean antibody levels in monkeys**			
	DPT polio vaccine		*Poliomyelitis vaccine*	
Type	*Level*	*Log_2 level*	*Level*	*Log_2 level*
1	⩾ 67**	⩾6.06	⩾ 34	⩾5.10
2	⩾140	⩾7.13	⩾116	⩾6.86
3	⩾105	⩾6.72	⩾ 63	⩾5.98

*10-16 animals used in test of each vaccine lot.
**Reciprocal of serum dilution.

as DPT Polio Vaccine, were prepared for further stability studies, and in such a manner that any lot showing suitable characteristics might ultimately be used for clinical trials. The formalin-inactivated poliomyelitis vaccine component, containing benzethonium chloride 1:40,000 as a preservative, was from a lot previously released by the Laboratory of Hygiene, Ottawa, for general distribution. To this were added ultrafiltered, concentrated formol diphtheria and tetanus toxoids specially prepared with benzethonium chloride 1:20,000 as a preservative, and concentrated *H. pertussis* vaccine prepared in a manner similar to that used for general distribution but with benzethonium chloride as a preservative. The final product contained, in each ml., 40 Lf diphtheria toxoid, 8 Lf tetanus toxoid, 15,000 million *H. pertussis* in phase 1, and 0.92 ml. trivalent, formalin-inactivated poliomyelitis vaccine.

In Table I are summarized data on comparisons of the potencies, in monkeys, of 10 lots of poliomyelitis vaccine, and the poliomyelitis vaccine components of the DPT Polio Vaccines prepared from corresponding lots. The serum levels shown are the reciprocals of the geometric means of the titres produced in monkeys. These are also expressed as logarithms to the base 2.

From the table it can be seen that DPT Polio Vaccine produced somewhat higher levels for each type than did poliomyelitis vaccine alone. However, the difference is significant at the 5% level ($t = 3.2$, $P < 0.02$) for type 1 only.

In Table II are shown the results of stability tests on the lot of DPT Polio Vaccine used in the clinical trial. These data show no loss of potency over a period of 14 months at 4° C.

CLINICAL TRIAL

The lot for which data are presented in Table II was selected for clinical trial on the basis of its stability at six months and its suitability for other reasons. It had been held for eight months at 4° C. by the time the first dose was administered in the trial and 10 months when the last dose was given.

TABLE II.—STABILITY OF POLIOMYELITIS VACCINE COMPONENT IN DPT POLIO VACCINE

Age of DPT polio vaccine (months)	*Number of animals*	*Log_2 of geometric mean antibody level in monkeys*		
		Type 1	*Type 2*	*Type 3*
0	6	6.33 ± 1.03	6.83 ± 1.03	⩾ 7.17 ± 1.38
6	16	⩾ 5.75 ± 0.45	⩾ 7.25 ± 0.37	⩾ 5.75 ± 0.80
11	16	4.17 ± 0.72	6.38 ± 0.62	4.63 ± 0.98
14	16	⩾ 6.50 ± 0.35	⩾ 8.16 ± 0.36	⩾ 8.25 ± 0.33

Through the co-operation of Dr. Lloyd A. Clarke, Medical Officer of Health, and Dr. John S. Kitching, Deputy Medical Officer of Health of Hamilton, Ontario, the trial was carried out in one of their immunization clinics. Fifty-one infants received 3 doses of the DPT Polio Vaccine. Of these, 12

*Presented in part at the 35th Annual Meeting of the Canadian Pædiatric Society, St. Andrews-by-the-Sea, N.B., June 13, 1958; and the 26th Annual Meeting of the Laboratory Section, Canadian Public Health Association, Montreal, Que., December 16, 1958.

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TABLE III.—RESPONSE (PERCENT CONVERSION) TO POLIOMYELITIS VACCINE AND TO DPT POLIO VACCINE PRIMARY VACCINATION—Q SERIES (INFANTS 3-12 MONTHS)

Series	Total in Series	Negative to type 1 Ratio	%	2 Ratio	%	3 Ratio	%
DPT polio; polio vaccine (72)	51	23/24	= 96%	24/24	= 100%	24/24	= 100%
Control polio vaccine only (72)	8	5/5	= 100%	5/5	= 100%	6/6	= 100%
K_2 series polio vaccine only (49 or 58)	54	26/35	= 74%	33/33	= 100%	32/41	= 78%
				Tri-negative			
DPT polio; polio vaccine (72)	51	12/13	= 92%	13/13	= 100%	13/13	= 100%
Control polio vaccine only (72)	8	4/4	= 100%	4/4	= 100%	4/4	= 100%
K_2 series polio vaccine only (49 or 58)	54	13/19	= 68%	19/19	= 100%	16/19	= 84%

K_2 series—2 doses (lot 49 or 58) DPT polio and control (lot 72)—3 doses

were three months of age, 21 were four months, 6 were five months and the remaining 12 were evenly distributed over 6-12 months. Owing to restrictions imposed by the available infant population in that locality, only 8 controls received poliomyelitis vaccine alone from the master lot used in the preparation of the DPT Polio Vaccine.

Each infant received three doses of DPT Polio Vaccine, or poliomyelitis vaccine alone, at intervals of four weeks. Those under six months of age received 0.5 ml. for the first dose and two additional doses of 1.0 ml. Those over six months received three doses of 1.0 ml. No undue reactions were observed. Blood samples were obtained from each infant before immunization and 14 days after the third dose. These samples were assayed for antibodies to the three types of poliovirus, and diphtheria and tetanus antitoxin titres were determined. Studies of agglutination titres for *H. pertussis* were given lowest priority and have not yet been completed in those cases where serum samples remain after the other assays.

TABLE IV.—DPT POLIO VACCINE. DIPHTHERIA ANTITOXIN TITRES: Q SERIES (51 INFANTS 3-12 MONTHS)

Units/ml. serum	Pre-immunization number of samples	14 days Post-immunization number of samples
<0.01	29	5*†
= or > 0.01	22	46
= or > 0.1	2	36
= or > 1.0	1	14

*All had maternal antibody of > 0.01 < 1.0.
†Retitration of these 5 samples:
3/5 < 0.001
1/5 = or > 0.008
1/5 = or > 0.002

Fig. 1 shows the percentage distribution of poliomyelitis antibodies to the three types of poliovirus before and after initial vaccination. The vertical line over the histogram of each type indicates the median level for the 51 infants. Before vaccination, approximately 50% of infants possessed antibody which was undoubtedly of maternal origin, especially in those under 6 to 8 months of age. After vaccination there was a marked shift in antibody level. The median level rose from 4 to 64 in type 1 and from 4 to 128 in types 2 and 3.

Table III shows the percentage of infants originally without antibody (negative in a dilution of 1 in 4) either for a single type (negative for type) or for all three types (triple negatives) who developed antibody upon vaccination. Of those negative for type, only one infant failed to respond to type 1; all responded to types 2 and 3. An identical picture is shown in the triple negatives. This response is significantly better for types 1 and 3 than in the K_2 series[1] where the infants received only 2 doses of poliomyelitis vaccine alone for initial immunization. All infants responded to the three types after vaccination with the control lot of poliomyelitis vaccine from which the DPT Polio Vaccine was prepared, but the numbers are too small for comparisons.

Table IV presents the diphtheria antitoxin titres before and after immunization. A significant number (25) showed a maternal antibody level of 0.01 unit or more before vaccination. Five of the infants failed to achieve a level of 0.01 unit 14 days after the third dose.

All infants responded to tetanus toxoid (Table V). The protective level is generally accepted as being ± 0.1 unit per ml.; 90% of the infants exceeded this by 10-fold to 1000-fold or more. The one infant with maternal antibody responded well.

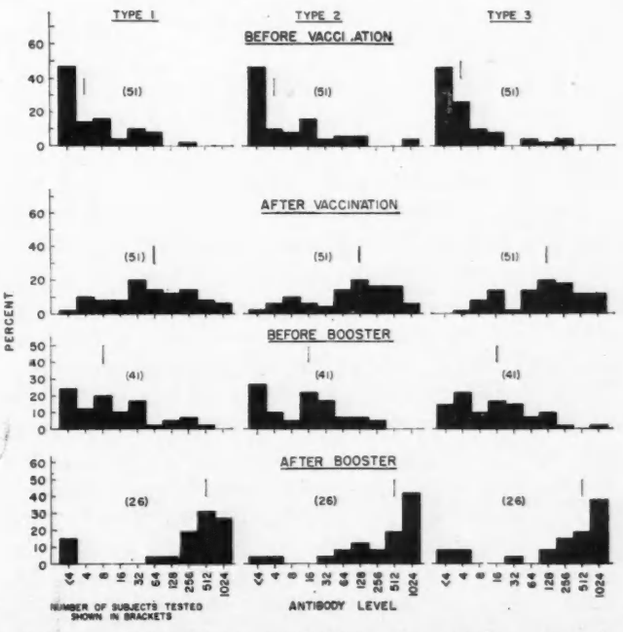

Fig. 1.—Percentage distribution of poliovirus antibody levels: infants 3 to 12 months of age given DPT Polio Vaccine (Q series).

TABLE V.—DPT POLIO VACCINE. TETANUS ANTITOXIN TITRES: Q SERIES (51 INFANTS 3-12 MONTHS)

Units/ml. serum	*Pre-immunization number of samples*	*14 days Post-immunization number of samples*
<0.1	50	0
= or > 0.1	1*	51
= or > 1.0	0	46
= or > 10		23

*Rose to > 1 < 10

RESPONSE TO A RECALL DOSE

Twelve months after the initial course of three injections, a fourth dose, 1.0 ml., of DPT Polio Vaccine was administered. Of the original 51 infants, blood samples were obtained from 41 before the recall dose, and from 26 two to three weeks after the recall dose. From Fig. 1 it may be seen that 12 months after the initial three doses of DPT Polio Vaccine there were small declines in antibody levels. For type 1, 76% had a titre of > 4, for type 2, 73% and for type 3, 85%. The median titres dropped from 64 to 8 for type 1 and from 128 to 16 for types 2 and 3.

TABLE VI.—DPT POLIO VACCINE. Q SERIES (INFANTS 3-12 MONTHS): INFANTS FAILING TO RESPOND AFTER RECALL DOSE.

Subject No.	*Age at vaccination*	*Specimen**	*Antibody Titre Type 1*	*Type 2*	*Type 3*
QB 7.....	5 mo.	A	256	⩽1024	64
		B	64	256	64
		C	<4	<4	<4
		D	<4	<4	<4
QB 10.....	3½ mo.	A	64	32	4
		B	16	8	16
		C	<4	<4	4
		D	<4	64	256
QB 27.....	12 mo.	A	<4	<4	<4
		B	<4	64	128
		C	<4	4	16
		D	<4	⩽1024	256
QB 30.....	2½ mo.	A	64	16	64
		B	4	4	16
		C	<4	<4	<4
		D	<4	32	<4

*Specimen A—pre-vaccination
B—post-initial vaccination
C—pre-recall
D—post-recall

After the recall dose (Fig. 1) the median titre rose from 8 to 512 for type 1, and from 16 to 512 for types 2 and 3. Fifteen per cent of infants failed to respond to type 1, 4% to type 2 and 8% to type 3. In Table VI are shown those infants who failed to respond. In each instance maternal antibody was present before immunization in a titre of 1:64 or greater, except in No. QB 27, an infant of 12 months, who was initially triple negative and who failed to respond to type 1, either after initial immunization or after the recall dose.

In Table VII are shown the diphtheria antitoxin titres of 38 of the original 51 infants one year after initial immunization. Seven had less than 0.01 unit and 31 more than 0.01 unit. In only 23 of these infants was a post-recall sample obtained. The five infants with less than 0.01 unit

TABLE VII.—DPT POLIO VACCINE. DIPHTHERIA ANTITOXIN TITRES: Q SERIES (INFANTS 3-12 MONTHS). RESPONSE TO RECALL DOSE 12 MONTHS AFTER PRIMARY IMMUNIZATION

Units/ml. serum	*No. pre-recall specimens—38*	*No. post-recall specimens—23*
<0.01	7 (5)*	0
= or > 0.01	31 (18)	23
= or > 0.1	14 (7)	23
= or > 1.0	1 (1)	22
= or > 10.0	1 (1)	19

*Figures in parentheses represent the number of infants from whom both pre-recall and post-recall specimens were obtained.

responded to the recall dose; all had more than 0.1 unit, 22 out of 23 had 1.0 unit or more and 19 out of 23 had 10.0 units or more.

One year after initial immunization only one of 35 infants had less than 0.1 unit tetanus antitoxin (Table VIII). All responded well to the recall

TABLE VIII.—DPT POLIO VACCINE. TETANUS ANTITOXIN TITRES: Q SERIES (INFANTS 3-12 MONTHS). RESPONSE TO RECALL DOSE 12 MONTHS AFTER PRIMARY IMMUNIZATION

N.I.H. units /ml. serum	*No. pre-recall specimens—35*	*No. post-recall specimens—22*
<0.1	1 (1)*	0
= or > 0.1	34 (20)	22†
= or > 1.0	10 (6)	22
= or > 10.0	2 (2)	18
= or > 100.0	0 (0)	8

*Figures in parentheses represent the number of infants from whom both pre-recall and post-recall specimens were obtained.
†Post-recall specimen only from one infant.

dose and attained a titre of at least 1.0 unit. Of the 22 infants 18 had 10 units or more and 8 had 100 units or more.

EFFECT OF MATERNAL IMMUNITY

The relationship of maternal antibody at the time of initial vaccination to the results after a recall dose of DPT Polio or poliomyelitis vaccine (controls) is shown in Table IX. After six months of age maternal antibody had, for the most part, disappeared. There was a slightly higher percentage response in those infants with no maternal antibody. This is most evident in the age group 2 to 5 months.

TABLE IX.—RESPONSE TO VACCINATION IN INFANTS AT DIFFERENT MONTHS OF AGE WITH AND WITHOUT MATERNAL ANTIBODY. THREE DOSES DPT POLIO VACCINE OR POLIO VACCINE WITH RECALL DOSE ONE YEAR LATER

	Proportion positive (conversion) 14 to 21 days after recall dose					
	Initially negative to type			*Initially positive to type (maternal antibody)*		
Age in months	*Type 1*	*Type 2*	*Type 3*	*Type 1*	*Type 2*	*Type 3*
2-5	9/9	11/11	11/11	13/16	13/14	12/14
6-8	2/2	1/1	1/1	—	1/1	1/1
9-12	3/4	3/3	4/4	—	1/1	—
Total 2-12	14/15 =93%	15/15 =100%	16/16 =100%	13/16 =81%	15/16 =94%	13/15 =87%

DISCUSSION

The age at which immunization with DPT Polio Vaccine should be initiated is determined by the desire to achieve immunity to whooping cough as early as possible. At three months of age a considerable proportion of infants (in this series between 40 and 50%) possess maternal antibody to both poliomyelitis and diphtheria. While the antibody levels after primary immunization were highly satisfactory, it was not possible to determine with any degree of accuracy, in those possessing maternal antibody initially, what proportion of the antibody after vaccination was maternal or actively acquired. One year after the initial series it was evident that a small number of infants had very low levels of antibody against the three types of poliovirus and less than 0.01 unit of diphtheria antitoxin. Even the tetanus antitoxin levels had declined, one infant showing a titre of less than 0.1 unit; here maternal antibody was not a factor. After the recall dose, it was evident that although levels had declined, the infants were sensitized by the initial immunization to respond to the recall dose; 85% responded to type 1 poliovirus, and over 90% to types 2 and 3. The response to diphtheria and tetanus toxoids was 100%, the majority possessing high titres. Since agglutinin titres to *H. pertussis* are not a significant measure of immunity, these determinations were given lowest priority and in most instances insufficient volumes of serum remain to carry out this procedure.

While it is evident from these data that maternal immunity may interfere, in some measure, with the responses to poliomyelitis vaccine and to diphtheria toxoid, it is also evident in the case of diphtheria toxoid that this interference may be overcome by the use of a good antigen initially, since pertussis vaccine acts as an adjuvant to diphtheria toxoid, and by the administration of an additional dose spaced some months after the initial series. It is also evident that while this additional dose is in the nature of a recall or reinforcing dose, it must be considered as an essential part of the establishment of good immunity in infants.

This trial was carried out under rigorous conditions. The first dose in those under six months was reduced to 0.5 ml. and the fourth dose was administered a full 12 months after the initial series. While it has been suggested in the past, in the case of DPT, that the first dose *may* be reduced to 0.5 ml. for infants under six months if it is desired to reduce reactions, it may be well to use the full 1.0 ml. dose, in the case of DPT Polio Vaccine, in order to increase the effectiveness of the type 1 poliovirus antigen and to administer the recall dose less than one year after the initial series. In addition it is evident that every effort must be made to increase the amount of type 1 antigen in poliomyelitis vaccines. This investigation is already under way.

SUMMARY

A stable "quadruple" antigen, DPT Polio Vaccine, has been prepared. The response of infants, the majority under six months, to three doses, followed by a fourth dose 12 months after the primary series, was highly satisfactory. Eighty-five per cent responded to type 1 poliovirus, and over 90% to types 2 and 3; 100% responded well to diphtheria and tetanus toxoids.

While the presence of maternal immunity interfered in some measure with the response to poliomyelitis vaccine and to diphtheria toxoid, the fourth dose, administered 12 months after the initial three doses, elicited the recall type of response and established a sound immunity.

The fourth dose, or first recall dose, must be considered essential in establishing immunity in infants.

The first dose of DPT Polio Vaccine should not be reduced in infants under six months, in order not to diminish the volume of the type 1 poliomyelitis vaccine component.

REFERENCE

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RÉSUMÉ

Les laboratoires de recherches médicales Connaught ont réussi à mettre au point sous forme stable un antigène quadruple comprenant de l'anatoxine antidiphtérique et antitétanique combinée à du vaccin antipoliomyélitique et anticoquelucheux. L'immunité conférée par trois injections de ce quadrivalent chez des nourrissons, suivies d'une quatrième un an plus tard, fut très satisfaisante. On trouva des anticorps I dans 85% des sujets et des anticorps II et III dans 90%. La réponse à la diphtérie et au tétanos fut de 100%. Bien que la présence d'anticorps maternels s'interposa dans une certaine mesure à l'action du vaccin antipoliomyélitique et de l'anatoxine antidiphtérique, la quatrième injection administrée douze mois après les trois injections du début produisit un effet de rappel et établit une immunité solide. Cette quatrième injection est donc une partie essentielle du programme d'immunisation, chez les enfants. Chez les nourrissons de moins de six mois la dose entière d'antigène quadruple doit être administrée afin de ne pas diminuer la portion d'antigène type I de la poliomyélite.

MEDICAL SOCIETY INSTALS DRUG STORE READING RACKS

Doctors' reception rooms aren't the only good places for distributing medical public relations literature. The Medical Society of the State of Pennsylvania is working with the state pharmaceutical association to use drug stores as additional distribution centres. When a local pharmaceutical association expresses interest in pamphlet distribution, the state medical society dispatches a representative to explain the program to the group. If the druggists agree, each member is supplied with a pamphlet rack and a quantity of pamphlets to display in his drug store. The society replenishes the supply periodically with up-to-date materials.

The whole operation is carefully coordinated with the state pharmaceutical association. That organization notifies its county groups of the program through its own publications and relays their interest back to the medical society. The state pharmaceutical association also supplies mailing lists and advises the medical society when to restock the druggists' literature.

It's all part of Pennsylvania's "Safeguard Your Health" educational program. TV and radio stations, newspapers, doctors' offices and now drug stores are being utilized to build a health education system that reaches almost everyone in the state.—*The PR Doctor* (Communications Division, American Medical Association), May 1959.

Canad. M. A. J.
Sept. 15, 1959, vol. 81

NUTRITIONAL EXCESS IN INFANCY AND CHILDHOOD*

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FOR MANY DECADES great emphasis has been placed on nutritional deficiency—quantitative and qualitative. In the child, the increased needs of the growing organism will quickly result in a deficiency state if certain nutritional requirements are not met. The rapid increase in world population, with dietary insufficiency in certain areas, has resulted in an increased interest in the nutritional handicaps of infants and children in these areas. The clinical picture of malignant malnutrition or kwashiorkor reported from Africa, India and Mexico is now well documented. However, in certain parts of the world malnutrition or undernutrition is no longer a problem, and perhaps in these areas our interest should be turned toward the possible hazards of overnutrition.[1]

It is now generally accepted that obesity contributes greatly to the development of coronary occlusion, atherosclerosis, hypertension and diabetes mellitus and to a shortening of the normal life span in the human adult. Dietary restriction of certain fats and an increased intake of protein are advocated by many physicians.

If overnutrition and overweight are harmful to the adult, is it not possible that these could also be harmful to the child? The case of overfeeding has been known for some time. Actually some physicians classify overfeeding as a form of malnutrition.

Recently Johnson, Burke and Mayer[2] in the United States have reported in a survey that 10% of the child population can be classed as definitely overweight. Generally the older clinicians in the past were convinced that the fat infant tolerated certain diseases poorly when compared to his thinner counterpart. Such diseases as gastrointestinal and pulmonary infections are tolerated poorly by obese infants, while eczema and asthma in infancy are often improved with a reduction in body weight.

Baumgartner[3] has shown that although there is an increased mortality in newborn infants with low birth weights there is also a greater mortality for the large, heavy newborn infant.

Today mothers are being constantly bombarded with advertising suggesting that bigger babies are better babies. Pædiatricians are not altogether free from blame, for many encourage the feeding of solid foods almost before the umbilical cord has been tied. Indeed a recent survey in the U.S.A. showed that a large number of pædiatricians placed their infants on most foods by 6-8 weeks of age. Some commercial companies advertise the superior value of their product because of the addition of vitamins or certain amino acids to supplement the infant's diet for the promotion of growth.

The effect on the mother of all this is that if the infant has not gained at least 1 to 2 lb. a month she is upset and suspects the inability of her physician to recognize some abnormality in her child to account for his "poor weight gain". Parents frequently compare their own child to those of the neighbours, and more than one father has been disappointed in his son because of his small stature, forgetting that he himself may be below average size. The parents then proceed to administer large amounts of milk, vitamins and tonics, etc., to "promote growth".

Today the infant and child is bigger and grows faster than his counterpart of 50 years ago. The old dictum that a child should double his birth-weight at six months and triple it by a year frequently does not apply to today's children, as many have doubled their birth-weight by three to four months. Meredith[4] has concluded that a one-year-old infant is 7% taller than his 19th century counterpart, although the difference in length at birth is only 1%. Boys 9 to 14 years old are 6-8% taller and 12-15% heavier than formerly. Is this due to better nutrition or lessening of disease, genetic factors, or is it merely "hybrid vigour" or possibly related to better socio-economic conditions?

One might for a moment consider the effect on potential longevity of this rather striking increase in the weight and height and rate of growth of today's child. It is quite conceivable that changes in the rate of growth would not materially affect length of life, because the process of ageing and senescence would proceed at their predetermined rates. However, it is possible that the rate of growth as such might determine the rate of ageing and thus the duration of life. Accelerated growth might cause excessive expenditure and premature exhaustion of energy and thus a shorter life. Generally the life span of lower animals may be prolonged by restriction of food with reduction in body size or of vital activities. However, higher species with complex organization are, during the growth period, less adaptable to drastic food restriction than lower forms of animal life. More important is the fact that we do not know at what age dietary restriction should be instituted in order to accomplish an optimal effect.[5] Is it possible that dietary restriction should begin in the age of infancy?

In considering the effect on longevity of present-day infant diets and feeding habits, one must not forget that today's adults reaching 65 or 75 years of age were more commonly fed in infancy a diet lacking in vitamins and "proper nutrition" rather than an excess. Therefore it will not be possible to assess the relationship of present-day diets to

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Presented at the Nutrition Conference, Dalhousie University, Halifax, Nova Scotia, March 12-14, 1959.

longevity for another 30 to 50 years, when today's infants and children have become older adults.

In encouraging maximum growth the parent and frequently the physician confuse maximum growth with optimal nutrition. One may ask of so-called "optimal nutrition"—optimal for what? Do we seek the best diet or optimal nutrition for maximal growth, or freedom from disease, or postponement of death, or fitness for work or war, or reproduction, or even for cultural achievement? We must remember that there is no satisfactory mathematical model for the curve of human growth and that human growth data are empirical.

Not only are today's infants probably receiving an unnecessary amount of calories in the form of excess fat and carbohydrate, but one must also consider the possible harm from over-administration of certain specific substances.

Of interest is the finding that breast milk contains significantly smaller amounts of dietary essentials than cow's milk. The average breast-fed infant for the most part receives less of these essentials than the U.S. National Research Council recommends. Tetany of the newborn occurs almost exclusively in the artificially fed baby as a result of the ingestion of the high phosphorus content in cow's milk.

Many nutritionists are suggesting the value of increased protein in the diet of the young infant. Recent work by May[6] would suggest that the increased intake of protein in the infant's diet does not necessarily increase the percentage of protein in the body composition. Harmful consequences have not been observed with increased protein in infant feeds except when water is lacking for the excretion of accumulated nitrogenous waste. However, experiments in young rats by Kennedy[7] reveal that pathological lesions ordinarily seen in the kidneys of aged rats are made to appear at a much earlier age by as little as a two-fold increase in the load of protein. Is it conceivable that this could happen to the young infant on a high protein intake?

One fascinating disorder that has been reported primarily from Great Britain and Switzerland is the so-called idiopathic hypercalcæmic syndrome. This is a disorder of calcium metabolism occurring in young infants and resulting in multiple signs and symptoms. These include abnormal development both physically and mentally, constipation, vomiting, abnormalities of kidney function and elevated blood pressure. The blood calcium level is found to be high. In comparison with the large number of cases in Great Britain, there is a marked lack of cases on this continent. A number of causes have been suggested but there exists a strong opinion that the syndrome is partly due to the excess ingestion of vitamin D.

British cod liver oil has approximately twice as much vitamin D as our preparation, and precooked cereals are fortified with vitamin D. In Britain, proprietary milk products contain 3½ times the amount of vitamin D used in this country.[8] It is of interest that increases in fortification of British foods were effected just a few years before the first reports of this syndrome, and an analysis of the foods revealed a higher content of vitamin D than stated on the label—presumably to allow for deterioration.

In Canada, case reports of idiopathic hypercalcæmia have been rare, only one case having been reported by Haworth.[9] It is quite likely that other cases have existed but the symptoms have not been recognized. Certainly with the commercial pressure for the addition of vitamin D to milk and food substances and the tendency for increased concentration of vitamin D in vitamin preparations, one might expect an increase in the number of idiopathic hypercalcæmia cases in the not too distant future.

In the particular case described by Haworth,[9] the high content of calcium in the drinking water was mentioned. It is attractive to consider the possibility that some of these cases might be due to increased calcium ingestion, and this would warrant further investigation.

Vitamin A is unquestionably toxic when given in large doses and may produce loss of hair, painful swellings of the skin, convulsions and enlargement of the liver.

More recently evidence has been presented of the toxic effect on young newborn infants of giving large doses of vitamin K, not only to infants at birth,[10, 11] but also to mothers just before delivery.[12]

The rather interesting finding of apparent injury to the newborn infant as a result of the administration of large doses of vitamins to the mother is of particular interest. Not only has vitamin K been implicated but also vitamin B_6. Hunt *et al.*[13] reported in 1954 a case of pyridoxine "dependency" in a newborn child who had recurrent convulsive seizures and progressive mental retardation. The mother had received rather large amounts of vitamin B_6 during her pregnancy and the authors suggested that the infant might be pyridoxine-dependent since the seizures were only controlled with 2 mg. of pyridoxine daily.

The tendency today to encourage the ingestion of extra vitamins during pregnancy might be considered in the light of the possible harm that might be done to the newborn infant.

The apparent rise in the incidence of scurvy in Canada has been discussed by Whelen *et al.*[14] This excellent paper comments on the fact that of the 79 cases reported, 80% of the cases received no vitamin C supplement, but 20% of the cases did receive vitamin C according to the family history. Although many of the cases were from economically poor homes, others were from the higher social and economic strata and were under the care of private physicians. Although there is no authenticated instance of "vitamin C resistant" scurvy, one might wonder if some of the 20%

cases described could be "vitamin-C-dependent". Could it be possible that some of the infants developed scurvy because of a greater requirement for vitamin C as a result of a high vitamin C intake by the mother during pregnancy? It would be interesting, although difficult, to attempt to assess the vitamin C intake of the mothers of this latter group, not for insufficient intake but for evidence of excessive ingestion of vitamin C.

The apparent increase in height and weight of today's children in comparison with the normal 19th century specimens raises the question whether yesterday's children were undernourished or whether today's children are overfed and overweight. Considering the possibility that infants and children of today are overfed and overnourished, we might ask if this can be harmful. McCay[15, 16] has demonstrated in rats that overfeeding with resultant overweight and overdevelopment results in an earlier death. As yet however, there is no large body of evidence to suggest that childhood obesity in the human is harmful.

Today the control of infections and the increased knowledge of nutritional requirements has resulted in a marked improvement in the health and growth of children. However, the present era is also conducive to overnutrition because of widespread promotional advertising and the general availability of potent dietary supplements. Optimum nutrition for the growing infant and child will therefore remain a challenge. The physician, dietitian and nutritionist must be aware of the possible harm from excess ingestion of all food substances by the young growing organism. It is not impossible that future pædiatric care may be concerned as much with nutritional excess as with nutritional deficiency.

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RÉSUMÉ

L'enfant dénutri voit son pendant en certaines parties du monde dans l'enfant suralimenté; il n'est pas impossible que les questions que soulève celui-ci en viennent à prendre autant d'ampleur que les problèmes que pose celui-là. L'obésité peut être aussi néfaste à l'enfant qu'à l'adulte. L'enfant gras résiste moins bien aux dérangements gastro-intestinaux et aux infections pulmonaires que son frère maigre et l'on a remarqué que l'asthme et l'eczéma s'améliorent souvent par simple amaigrissement du jeune malade.

Les mères de famille sont soumises à un barrage de publicité de produits alimentaires et commencent à s'inquiéter si le marmot ne gagne pas son kilo par mois. Les enfants d'aujourd'hui croissent plus rapidement que ceux du siècle dernier mais vivront-ils aussi longtemps? L'auteur s'étend en conjectures sur la relation entre le taux de croissement et le taux de sénescence. En effet les adultes d'aujourd'hui qui atteignent un moyenne de longévité de 65 à 75 ans furent nourris à l'ancienne manière, le plus souvent sans apport vitaminique supplémentaire. La nutrition prétendue "idéale" est la meilleure à quelle fin? Les tableaux de relations entre le poids, la taille et l'âge ne sont qu'empiriques et n'expriment que les dimensions du plus grand nombre d'individus. Il est intéressant et instructif de comparer la teneur en substance nutritive et en minéraux du lait de vache et du lait humain; ce dernier contient une moindre quantité de substances dites essentielles. On a récemment décrit en Angleterre et en Suisse un syndrome connu sous le nom d'hypercalcémie idiopathique, atteignant les nourrissons. La forte teneur en vitamine D de certaines préparations polyvitaminiques pour les enfants employées dans ces pays en serait-elle responsable? L'abus de vitamines A et K peut aussi porter non seulement sur les enfants mais aussi sur les femmes enceintes. L'auteur introduit la notion de dépendance aux vitamines relevant de l'assuétude. Il termine en se demandant si l'on suralimente les enfants.

LES SIGNES FONCTIONNELS QUI PERMETTENT DE SUSPECTER UNE NEPHRITE ASCENDANTE

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CES DERNIÈRES ANNÉES, le développement de nos moyens d'investigation nous a permis, dans un nombre croissant de cas, de découvrir l'étiologie, jusqu'à présent ignorée, de syndromes néphrotiques, de néphrites chroniques ou d'hypertensions artérielles. Parmi les causes de ces trois syndromes, la plus fréquente nous paraît l'infection urinaire ascendante.

La recherche des signes classiques d'infection urinaire aiguë ou chronique est bien connue, mais à côté de ces signes fonctionnels la confrontation entre les signes cliniques, les données biologiques, radiologiques et anatomiques nous a permis d'attacher une valeur de plus en plus grande à un certain nombre de manifestations dont l'importance réelle n'a pas été signalée. Ces signes sont: la connaissance de poussées fébriles inexpliquées; une énurésie nocturne de l'enfance; une pollakiurie diurne et nocturne, une soif intense; des anomalies de la miction.

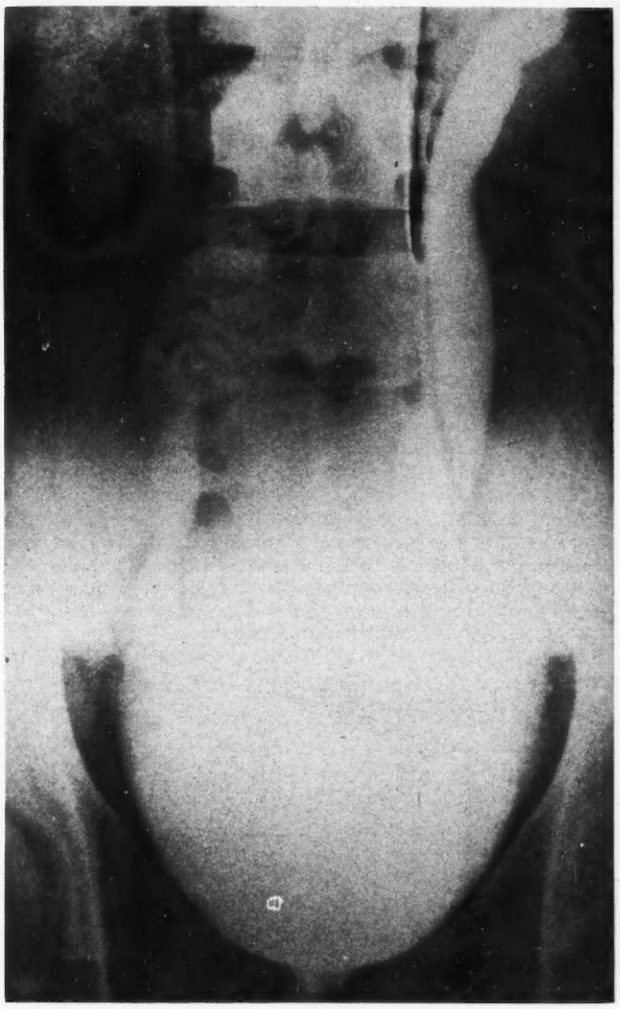

Fig. 1.—Cystographie par voie basse. Reflux urétéral bilatéral lors des efforts de miction.

La découverte de l'un de ces symptômes doit faire chercher systématiquement un trouble urologique à l'origine d'une maladie rénale ou vasculaire.

Les poussées fébriles inexpliquées récidivantes.—Dans un certain nombre d'observations de néphrites chroniques d'origine ascendante, ce phénomène est le seul témoin rétrospectif d'accès d'infections urinaires aiguës n'ayant pas donné lieu à d'autres manifestations fonctionnelles. Ces poussées fébriles surviennent très brusquement et s'effacent en quelques heures. L'accès thermique est isolé, aucune autre manifestation ne permet de l'expliquer. L'entourage se souvient parfois que les urines répandaient une odeur nauséabonde.

L'énurésie de l'enfance.—Sur nos 180 dernières observations, nous l'avons relevée 15 fois. Dans tous ces cas, sauf deux, existaient d'importantes malformations rénales ou urologiques jusque là méconnues (atrophie rénale dans la majorité des cas, hydronéphrose, maladie du col avec ou sans reflux urétéral). La fréquence de cet antécédent, son association avec d'indiscutables lésions organiques, permettent d'exclure formellement l'hypothèse d'une coïncidence. Cette énurésie dure jusqu'à un âge variable (4 à 10 ans) et elle est souvent suivie d'une pollakiurie nocturne, comme si l'énurésie cédait lorsque l'adolescent connaît un sommeil moins profond et est réveillé par le besoin d'uriner. Parfois cette énurésie est accompagnée d'une pollakiurie diurne et de polydipsie.

La *pollakiurie diurne et nocturne*, la *polydipsie* peuvent d'ailleurs exister isolément sans énurésie, sans fièvre, sans brûlures à la miction. Elles traduisent un trouble tubulaire distal de la réabsorption de l'eau. Lorsqu'elles existent depuis longtemps, ayant précédé de très loin l'apparition des signes patents de néphrite chronique et d'hypertension, elles constituent un argument très important en faveur d'une tubulopathie ancienne, primitive ou secondaire à des manifestations urologiques.

Les troubles fonctionnels se produisant lors de la miction attirent plus particulièrement l'attention vers une anomalie possible des voies excrétrices basses:

Le *"signe du reflux"* consiste en une douleur dans la fosse lombaire ou iliaque, d'intensité et de brutalité variables, survenant essentiellement lorsque le malade a envie d'uriner et plus encore au début de la miction. Cette douleur apparaît surtout lorsque le malade a attendu longtemps pour uriner ou "pousse" sur un sphincter hypertonique pour vider sa vessie. Cette douleur uni ou bilatérale, qui ne dure que quelques instants et disparaît dès la fin de la miction, traduit l'existence d'un reflux urétéral. La pratique de la cystographie mictionnelle nous a permis de confirmer cette pathogénie (Fig. 1).

La valeur d'une *"miction en deux temps"* nous a été enseignée par la radiocinématographie urinaire. Le malade a une miction normale et, quelques minutes plus tard, une nouvelle miction permet de recueillir 100 c.c. d'urine et parfois plus, alors qu'entre temps il n'y avait pas de résidu vésical, les urines secondairement excrétées avaient été chassées dans les bassinets et les uretères distendus. Cette miction en deux temps traduit donc elle aussi l'existence d'un reflux pyélo-urétéral. Il est rare cependant que la quantité d'urine ayant reflué soit suffisante pour déclencher immédiatement une nouvelle envie d'uriner: aussi faut-il rechercher systématiquement ce signe, en faisant uriner le malade deux fois à cinq minutes d'intervalle ou en le sondant deux fois quelques secondes puis quelques minutes après le première miction. Les troubles de la miction ne sont pas souvent signalés spontanément par le malade lui-même car, ayant eu depuis toujours des troubles mictionnels, il n'en connaît pas le caractère pathologique: l'interrogatoire doit donc en chercher systématiquement l'existence et tout particulièrement le signe de la *miction retardée.* Ce retard, cet effort lors de la miction témoignent d'un obstacle uréthral, d'une maladie ou d'une dyskinésie du col, se traduisant sur les cystographies par un aspect de vessie de lutte: vessie petite, globuleuse avec image de doubles contours, témoignant de l'épaississement du dé-

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trusor. En d'autres cas il y a atonie vésicale avec méga-vessie et diverticules.

Enfin, parmi les troubles mictionnels, il faut ranger un phénomène qui se produit surtout chez la femme: certains sujets, depuis leur enfance, ou n'éprouvent pas le besoin, ou se retiennent volontairement d'uriner, arrivant parfois à n'avoir qu'une ou deux mictions par jour. Il peut en résulter à la longue une dilatation vésicale et l'orifice urétéral peut se trouver forcé avec reflux secondaire. Dans de tels cas, si le trouble est découvert à temps, la simple rééducation vésicale avec mictions volontaires fréquentes peut suffire à obtenir un retour à la normale.

Ces différentes manifestations peuvent exister isolées ou associées. L'une quelconque d'entre elles doit faire chercher une anomalie urologique, par l'exploration instrumentale et radiologique, en recourant si possible à la radiocinématographie qui s'avère susceptible d'apporter des renseignements irremplaçables.

SUMMARY

A number of cases of renal or vascular disease are associated with an ascending urinary infection. The author describes four factors, whose presence should lead to suspicion of such an infection. The first factor is the history of febrile attacks, appearing suddenly and lasting for several hours, without other identifying signs. The second factor is a history of enuresis in childhood. In 180 observations on patients with chronic renal disease, such a history was obtained on 15 occasions. In all but two of the later, significant renal or urological malformations were discovered. In these cases the enuresis persists up to the age of 4 to 10 years, and may be followed by nocturnal frequency.

The third factor is a history of frequency of urination by day and by night, maybe associated with excessive thirst. This is a sign of disturbance of reabsorption of water from the tubules. Lastly, functional disturbances during micturition may draw attention to an anomaly in the lower urinary tract. Thus lumbo-iliac pain when the bladder is full may be due to a ureteral reflux, and the production of 100 c.c. of urine or more several minutes after a supposedly normal micturition is also suggestive. Moreover, a history of very infrequent micturition (once or twice a day) in females may be the result of long-standing dilatation of the urinary tract. In demonstrating the basis of these disturbances, radiocinematography is an indispensable aid.

SAVE A LIFE WITH A BREATH OF AIR

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SOME ELEMENTS of mankind are racing to convert the inventions of science to instruments of destruction and death, while others have begun the bewildering search for techniques and instruments of self-preservation. The latter has been a good trend in the widest sense, for it has aroused also a new approach to many old problems. Never before have the civilian population and their agencies been so loud in their demand for better methods of preventing serious injury and of restoring those who are near death. This change in attitude has also encouraged the application of new skill and knowledge to the techniques of resuscitation.

The past few years have seen an alteration in the approach to those dying as a result of a drowning accident, or serious automobile collision, to men trapped or struck down by a cave-in, and to victims of the multitude of accidents that can happen in the home, in the factory, in vacation-land, and even in hospitals. The deaths that occur in most of these situations are due in most instances to depressed breathing or partial occlusion of the victim's airway.

Anæsthetists recognize the importance of training other doctors and rescue teams in the simplest and the most reliable method of reviving the apparently dead by the administration of air or oxygen directly to the lungs through a clear airway. The anæsthetist is eminently qualified for teaching this procedure, because he is aware that the main problem in most severe injuries and in all comatose patients is that of partial obstruction of the airway, and *he always treats this first.* His daily work brings him face to face with such situations, whereas the average physician or rescue team encounters them only occasionally. For this reason, he is the most frequent consultant in serious emergencies which require restoration of adequate breathing.

To physicians through the ages, the idea of breathing for the unconscious by blowing air directly into the lungs has seemed the obvious and best method, just as in the Bible when Elijah revives an unconscious child by blowing air into its lungs. The words from *Kings* tell us: "And he went up and lay upon the child, and put his mouth upon his mouth, and his eyes upon his eyes, and his hands upon his hands: and he stretched himself upon the child; and the flesh of the child waxed warm."

In 1744, Dr. William Tossach in Edinburgh reported how he revived a cold, grey, limp miner just rescued from a smoke-filled mine. No pulse was detectable. Tossach said: "I applied my mouth close to his, and blowed my breath as strong as I could, but having neglected to stop his nostrils, all the air came out at them. Wherefore, taking hold of them with one hand, and holding my other on his breast, at his left pap, I blew again my breath as strong as I could, raising his chest fully with it. Immediately I felt six or seven very quick

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beats of the heart; his thorax continued to play and the pulse was felt soon after in the arteries." This method of artificial respiration was continued, and the miner was revived.

In 1850, Dr. Metcalfe of New York described the successful use of mouth-to-mouth breathing in one of his patients whose heart beat became inaudible during an operation under anæsthesia. Dr. Metcalfe held the patient's mouth open with the right hand and closed his nose with the left; after 20 inflations, the patient gasped and blood began to spurt from the artery.

One of the most famous references to the direct mouth-to-mouth method of resuscitation is the one in which Dr. Leale successfully prolonged the life of Abraham Lincoln after he was shot and critically wounded in 1865.

The method of mouth-to-mouth resuscitation of the dying victim has not taken hold over the years, for many reasons. During recent years, the excuse has been the fear of infection to the rescuer. However, the obvious reason is reticence or even repulsion from applying one's mouth to that of a stranger, especially when he appears to be dead or on the verge of death. This hygienic and æsthetic diffidence is the greatest stumbling block in teaching the public the direct method of resuscitation. For this reason, a wide variety of other techniques were devised for reviving the dying.

To Paracelsus (16th century) belongs the credit for inflating the lungs with a bellows connected to a tube inserted into the mouth of an asphyxiated patient. This method was used during the next two hundred years to maintain life in animals when operations were undertaken in the open thorax.

John Hunter, the surgeon, carried out experiments for restoring life to the drowned, and after 1755 he described a double-chamber bellows of his own invention for filling and exhausting the lungs of air as a method of resuscitation. Hunter's advice received commendation in an independent report by Dr. William Cullen of Edinburgh in 1776. He reported to the Royal Humane Society that inflation of the lungs with a bellows was a safe and reliable method of resuscitating drowned victims. Thereafter, the Humane Society reports the award of medals and other prizes to a great number of people for various devices for carrying out such a procedure. Some of these devices were the forerunner of the rubber oral airways designed by Gwathmey, Guedel and Waters, and now used by all anæsthetists.

In 1827, a series of papers was delivered to the French Academy of Sciences by LeRoy. He cast grave doubts on the safety of forced inflation of the lungs, carried out with a bellows. He demonstrated with practical experiments that, with the lips applied to the resuscitation cannula, forcible blowing could rupture the alveoli, causing emphysema and tension pneumothorax, with fatal results. It was his opinion that many patients, who otherwise would have recovered, were speedily dispatched by the overenthusiastic use of the bellows in the equipment then issued to the French police.

On account of the danger of the bellows then in use, LeRoy designed one which had a calibrated volume scale marked off according to the victim's age, in order to deliver a volume of air which was related to the victim's size. With this bellows, LeRoy claimed that damage to the lungs due to overinflation was unlikely to occur. Nevertheless, the practice of resuscitation by inflation of the lungs with a bellows fell into general disfavour. Even the Royal Humane Society no longer recommended the use of bellows which they had supplied for resuscitation.

During the past century (1850-1950) the direct inflation of the lungs as a method of resuscitation was seldom reported. During this period a variety of indirect methods (external stimulation) were employed. The idea of direct oral inflation, however, was revived sporadically by inventors such as Erichsen, whose apparatus was described in 1845. In the course of his paper, Erichsen stated "In those desperate cases in which submergence (drowning) has lasted for more than four minutes or in which there is no sign of vitality left, and in which the measures at present adopted are generally ineffectual, I would most strenuously recommend the trial of the inflation of the lungs with oxygen gas." He advised that the chest should be inflated with 15 cubic inches (250 ml.) of oxygen, ten times a minute, the chest and abdomen being depressed after each inflation. He stressed the danger of forcible inflation.

Erichsen's report was based on scholarly experimental investigations, and although he could not convince the Royal Humane Society, his work is now considered the cornerstone of experimental investigations into the problem of asphyxiation.

While medical leaders were debating the importance of artificial respiration directly through the mouth, resuscitation teams in various countries were already using a variety of indirect methods for artificial respiration. In Paris, the favourite method was manual compression of the chest and abdomen. In parts of England, the method consisted of rolling the victim either over a barrel or on the ground.

Dr. Marshall Hall of England on many occasions observed victims of drowning being trundled on the ground in an effort to resuscitate them. He keenly felt the need for a simple, effective method of artificial respiration which could be used even by men with no medical training.

At first, Hall experimented with lifting the shoulders of the victim, who was placed in the prone position, but he gave this method up as too strenuous and inefficient. After discontinuing the tests with the shoulder lift, Dr. Hall tried the "rolling method". He performed a few experiments on cadavers, and found that he was able to produce adequate pulmonary ventilation in this way.

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In his publication of 1856, the method described consisted of alternate rolling of the patient's body from prone posture to the side. A month after his original report, he published another article in which the method was slightly modified: an expiratory pressure on the back was added while the patient was in the prone position. He called this method the "ready" or "prone and postural" method. Treating the drowned in this way was widely advocated as the most important means of resuscitating a non-breathing person, but the difficulties of execution, and its ineffectiveness, became obvious after a short period of trials on actual drowning victims.

The great contribution of Hall lies in the wide dissemination of knowledge that manual artificial respiration can save lives. Various modifications of his method were introduced in Europe and in the United States during the next half century (1850-1900).

At the time when the arguments regarding the efficacy of various methods of artificial respiration and resuscitation were reaching their peak, and when Hall was turning the tide in favour of indirect (manual) artificial respiration, Dr. Henry Silvester became interested in this problem. He knew that Hall had tried to assist in both inhalation and exhalation during manual artificial respiration. In trying Hall's method, Silvester found that it was difficult to perform and it had little beneficial effect on the victim. He decided, therefore, to try the method of placing the victim on the back, raising both arms upward—to cause an expansion of the chest and inspiration, after which he replaced the arms on the chest and applied pressure for expiration.

Initially, those that compared the Hall method and the Silvester method favoured Hall's method because it started artificial respiration with an expiration, which cleared the air passages. In 1861, following a report in which the Hall method had been tried on 15 drowning victims, each time being unsuccessful, the Royal Humane Society abandoned the Hall method in favour of the Silvester method, and Dr. Silvester was made an Honorary Medical Assistant to the Society. Thereafter, the Silvester method rapidly gained recognition all over the world. With some modifications, it is still the method of choice in eastern Europe. It is also used by the Bureau of Mines in the United States.

In the latter part of the 1860's, Dr. Benjamin Howard had been teaching medical students and police both the Hall and Silvester methods. He realized that while the Hall method was cumbersome, the Silvester technique was also not simple to perform and was not always suitable in an operating room. Therefore, he devised a procedure in which artificial respiration was brought about by applying pressure on the lower part of the chest in order to cause an active expiration. Inspiration was achieved through the recoil of the chest to normal position. In the operating room this manœuvre was done with the operator standing at the side of the patient. His method fell into disrepute, however, after he broke a famous man's ribs (Sir Samuel Haughton) during a demonstration of his technique.

Although resuscitation teams in continental Europe seemed to be satisfied with the Silvester method, the English were not. In 1890, the Medical Society of London appointed a committee to evaluate the current methods of manual artificial respiration. Dr. Edward Schafer* carried out the assignment. He experimented on dogs first, and then on human beings. During the tests, his human subjects were requested to hyperventilate. After this action, breathing was usually suspended for a few minutes, during which time the volunteer had no subjective desire to breathe. During this period of apnœa, Schafer applied various methods of manual artificial respiration and measured the pulmonary ventilation by means of a spirometer. These experiments showed that the Silvester method gave the least ventilation, the Hall method was a little better, and the Howard method was the best of the three, *but none of the methods produced normal tidal exchange of air.* Because of these results, Schafer invented another method which he found to cause a larger pulmonary ventilation. He called this method the "'prone-pressure" method. It gained popularity in spite of initial opposition in England and continuous opposition in many European countries. In 1908, Dr. Schafer came to the United States to deliver his famous Harvey lecture on manual artificial respiration and showed that his method was efficient.

Even though Liljestrand and his co-workers made a careful study of the various methods for artificial respiration on living subjects in 1913, and found that the Schafer method was inferior to the Silvester method, the Schafer method was approved in the United States in 1914.

In Denmark, Schafer's method met with opposition from the medical profession, but found favour among life-savers. One of the experienced instructors in life-saving, Col. Holger Nielsen, who had been teaching the Silvester method, switched to the Schafer method in 1907. Twenty-three years later he published an article about the effectiveness of this method. This article created such a controversy that it spurred him on to find a new method of artificial respiration, which would combine the best features of the Silvester and Schafer methods, and would be superior to them. Since Neilsen believed that the supine position of the Silvester method is objectionable, he placed the subject in the prone position with the arms extended overhead, as Schafer had done. In this position the Silvester arm action was impossible. Lifting the extended arms backward was painful to the subject, and even dangerous to the point of dislocating the shoulder joints. To avoid this, he bent the elbows of the subject and placed the

*Sir Edward A. Sharpey-Schafer.

hands under the forehead. The inspiratory manœuvre now could be accomplished by lifting the elbows. This resulted also in a partial lift of the upper part of the subject's body. In 1932 Neilsen published an article describing his method, in which the elbows were raised to draw air into the lungs and then pressure was applied to the shoulder blades to cause a forced expiration. This method was approved by the Danish Red Cross in 1933. During the next few years it was adopted by all Scandinavian countries.

While Nielsen was devising his new method of manual artificial respiration, Dr. F. C. Eve of England re-discovered the old teeter-totter method, in which a drowning victim is strapped to a board in lying position (face down), and then is seesawed. The teeter-totter method received much support because of its apparent simplicity. It was adopted by the British Navy and gained popularity in the United States.

After World War II, there were still doubts among many people as to the best method of manual artificial respiration. Consequently the American Red Cross made grants to the University of Illinois in support of investigations under the direction of Dr. A. C. Ivy and Dr. Archer S. Gordon. With the co-operation of a team of experts, Gordon soon made two reports on pulmonary ventilation obtained by means of indirect (manual) artificial respiration. One report dealt with over 100 fresh corpses, and with human subjects who were made apnœic by voluntary overbreathing. The second report dealt with tests made on a group of volunteers whose respiration was arrested by means of sedatives and curare, and whose lives depended on artificial respiration.

In their study, Gordon and his co-workers tested the Silvester, Schafer, Nielsen, Eve, the hip-lift, the hip-lift prone-pressure, and the hip-roll prone-pressure methods. Both reports demonstrated that the prone-pressure method gave less pulmonary ventilation than the other methods used in the study. These two reports made a great impression not only on the medical world but also on laymen. They were widely publicized in newspapers and magazines and on television. In June 1951, the investigators and co-ordinators of this study met. After careful scrutiny of the experimental data regarding the effect on pulmonary ventilation, on blood oxygenation, on the circulation, and on the difficulties of execution, teaching and learning, the participants unanimously agreed that the Nielsen method was the method of choice, and that in second place was the hip-lift prone-pressure method. They recommended that back pressure should precede the arm lift in performing the Nielsen method in order to clear the airway initially.

Although the Nielsen method was widely accepted officially, there were still many who felt that this was not the final solution to the problem of artificial respiration. Perhaps the most important factor overlooked by Ivy and Gordon in carrying out these studies, and in analyzing the data, was that the efficiency of any of these methods in the field required an unobstructed airway. In carrying out their studies on paralyzed volunteers, the investigators had inserted an endotracheal tube which would assure patency of the airway. *Under field conditions, such assurance of a clear airway does not exist, and the efficacy of these methods would be much less than was found in their experimental situation.*

In 1953, Dr. James O. Elam and Dr. E. S. Brown reported to the American Army on studies carried out with direct mouth-to-mask methods of artificial respiration. They noted that these methods were easy to perform and universally more efficient than any indirect method of artificial respiration. In 1956, Dr. Peter Safar, in association with Dr. J. O. Elam, reported to the American Army on studies of the direct mouth-to-mouth methods and proved unequivocally that the direct mouth-to-mouth method of artificial respiration was by far the most efficient method of resuscitation under field conditions, provided that some simple rules of technique (such as were mentioned by Tossach in 1744) are carefully followed:

The victim is placed in the supine horizontal position immediately; the throat is cleared of secretions, vomitus, etc.; the head is tilted back into the "sniffing" position; the mouth is opened and the lower jaw is elevated with the thumb and index finger; the nostrils are pinched; and after the rescuer takes a deep breath, his parted lips must firmly seal the victim's open mouth; the rescuer then exhales into the mouth of the victim until the chest is observed to rise. The inflation procedure is repeated 10 to 15 times a minute until the victim begins to breathe adequately. If the stomach is observed to be filling with air, it should be expelled by gentle manual pressure on the upper abdomen.

This report reopened the controversy about satisfactory methods of artificial respiration, and in 1958 the mouth-to-mouth method of artificial respiration was officially adopted by the American Army and American Red Cross.

Just as occurred over 100 years ago, strong objections have been raised against applying the rescuer's mouth to that of the victim. During the past year, in addition to the Kreiselman hand bellows respirator, a variety of old devices have been redesigned and advocated for insertion into the mouth, or applied to the face, in order to separate the mouth of the rescuer from that of the victim. One is a combined self-inflating bag, non-rebreathing valve and face mask, designed by Dr. Henning Ruben. Another is a bag and face mask attached through an aluminum central axial body with two arms which contain small tanks of oxygen that can be perforated in order to inject the bag, designed by Dr. Robert A. Hingson. The simplest devices consist of two oral airways (of the Guedel type) joined together at their external flanges in

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an S shape, introduced by Dr. Peter Safar; a single oral airway with a blow-tube attached to the external flange, introduced by Dr. M. Brook; a simple blow tube with elliptical-shaped concave mouthpieces at both ends, introduced by Dr. R. A. Berman; and a plastic face mask which may be fitted snugly over the nose and mouth, and which has a short blow tube, introduced by Dr. J. O. Elam.

All of these devices require training for proper use. A face mask or concave mouthpiece may not be effective because it is difficult for the unskilled to ensure an airtight fit on the face while supporting the jaw properly. Non-rebreathing valves often stick and may cause obstruction to breathing. The insertion of an oral airway requires experience for proper placement, and may itself cause airway obstruction or initiate laryngeal spasm or vomiting if the victim is not unconscious at the time of insertion.

After a period of instruction and practice in their use, all of these devices are valuable additions to our equipment, and are excellent aids to resuscitation. However, their value depends completely on general availability. *In a serious emergency, wherever it occurs, the only equipment that the rescuer can be assured of, at a moment's notice, are his hands and his lips.*

EPILOGUE

A brief history of the methods of artificial respiration has been reviewed. Many learned men of medicine have studied these methods, and thousands of rescue workers have tried them. It is unfortunate that, until recently, the advantages and disadvantages of each method have not been delineated and publicized with more consideration of the vital factors of physique and physical state of the victim and the rescuer as they may occur under field conditions.

For the survival of a victim of any accident in which obstruction or depression of breathing has occurred, it is essential to consider: how quickly effective resuscitation can be applied, how well a clear airway is restored, and the minute volume of gas exchange that can be provided. The oxygen saturation of the blood, and the possibility of trauma to the chest wall or the ribs, are secondary considerations during the critical emergency.

For the rescuer, the method of resuscitation must be easy to learn and easy to apply in any type of situation without special apparatus, must require little energy to perform effectively, must be completely harmless, and should, if possible, avoid æsthetic or hygienic objections. In the collapsed non-breathing victim, the direct mouth-to-mouth method is without doubt the most effective way to restore life, and the mouth to oral airway or self-inflating bag with mask is the safest and most satisfactory method for those who have had limited instructions. Any other apparatus should be used only by those specially trained in resuscitation.

The indirect methods (Schafer, Nielsen, Silvester, etc.), using one or two operators, all produce some tidal exchange and one should not belittle these methods—for they have saved lives, and should still be used if nothing else is possible in special circumstances. However, if the victim is in an awkward position or cannot be moved, indirect (manual) methods cannot be used effectively. Even if the victim can be moved, the back pressure or chest pressure methods are ineffective if the victim is very obese, if the chest wall and lungs are very stiff (because of disease or the changes of aging), or if the chest wall is severely damaged or punctured. The indirect methods also become ineffective if prolonged resuscitation is required because the rescuer tires and he is unable to control the victim's airway, which tends to become obstructed by flexion of the head.

For the widest range of situations the direct methods are certainly the most efficient and should be taught in every centre across the country. This can be done very easily by the use of a plastic manikin. On such a device the lay public can be shown, very simply, the proper technique for carrying out effective resuscitation, either by the mouth-to-mouth method or by the mouth-to-airway method.

The most important points to remember about artificial respiration are that it must be started immediately, and that a patent airway must be maintained. If these two factors are assured, the reviving effect of fresh air rhythmically entering and leaving a victim's lungs soon becomes evident, if irreparable damage has not already affected the vital organs of the body.

The next important point to remember is well known but bears re-emphasis: If you cannot feel the pulse or heart sounds in the victim of a traumatic accident, drowning, electrocution or poisoning, it does not mean that death has taken place. Physicians (especially anæsthetists) have resuscitated many patients under such circumstances, and recovery has been complete. Drowning and electrocution victims have been resuscitated after more than 30 minutes of submersion or in deep coma from electrocution. They have also revived apparently dead persons after very severe drug poisoning. Regardless of whether the victim is a newborn child or an elderly person who has suffered from a medical catastrophe (e.g., coronary thrombosis), the heart and breathing rarely cease instantaneously, and an apparently dead person may have extremely depressed breathing for half an hour or more before the heart ceases to beat. It is only after both the breathing and the heart beat have ceased that one has only three to four minutes left in which successful resuscitation is possible. Even after this point is reached, one should always try to save a life with a breath of air.

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RÉSUMÉ

L'anesthésiste est sans contredit le spécialiste le mieux qualifié pour traiter les cas d'insuffisance respiratoire, surtout du genre causé par obstruction des voies aériennes. La méthode de respiration artificielle par insufflation pulmonaire remonte aux temps bibliques et l'auteur en retrace brièvement l'historique. L'air insufflé peut provenir indifféremment des poumons d'une autre personne ou d'un soufflet. Il décrit ensuite les principales méthodes de respiration artificielle par manipulation du thorax ou par changement de position de la poitrine. La méthode de Silvester, entrée en vigueur vers 1861, est encore employée couramment en Europe orientale et dans certains organismes des Etats-Unis. La méthode de Howard perdit sa popularité lorsque l'auteur fractura une côte de Sir Samuel Haughton qui s'était prêté comme sujet de démonstration. La méthode de Schafer devint à la mode et fut adoptée aux Etats-Unis en 1914. En 1933, les pays scandinaves adoptèrent la méthode de Nielsen dans laquelle un rehaussement des coudes produit un mouvement inspiratoire. La marine britannique adopta une méthode redécouverte par le docteur Eve, qui consiste à attacher le sujet à une planche et à faire basculer le tout comme une balançoire. Enfin, en 1958, le cycle entier fut complété: on revint à une méthode vieille de plusieurs centaines d'années qui consiste à insuffler les poumons en appliquant la bouche de l'opérateur sur celle de la victime le plus hermétiquement possible (le nez étant bouché) et à souffler l'air dans les voies respiratoires de celle-ci. Cette méthode qui se recommande par sa simplicité et son efficacité est maintenant en vigueur dans l'armée et le Croix-rouge américaines.

THE PYLORIC SEGMENT AFTER GASTROENTEROSTOMY*

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ALTHOUGH gastroenterostomy is now seldom performed for peptic ulcer disease, patients who had this operation many years ago are still seen. In some of these, a radiological configuration of the stomach has been encountered which has not been previously stressed. This consists of a narrowing of the pyloric antrum or of that portion of the stomach distal to the anastomosis. The recognition of this condition is important because the radiological findings may be confused with those in malignant disease.

Clinical, radiological and gastroscopic observations in seven male patients with this benign deformity will be discussed.

CASE 1.—R.L., aged 67, had a gastroenterostomy in 1919 after perforation of a duodenal ulcer. He continued to experience occasional epigastric pain and vomiting. A barium meal study in May 1956, showed a well-functioning gastroenterostomy (Fig. 1) and marked contraction of the pyloric segment "suggesting scirrhous carcinoma".

At gastroscopy the gastrojejunostomy stoma appeared normal. No angulus was seen. The pyloric segment was markedly contracted and cone-like. The mucosa of this segment appeared normal. The pylorus, which appeared atrophic, was clearly seen as a slit-like opening. In September 1957, he complained only of minimal epigastric pain and occasional vomiting. His appetite was good, and he was gaining weight and looked well. There were no significant abnormalities on physical examination. The hæmoglobin level and white blood cell count were normal. Erythrocyte sedimentation rate (Westergren) was 34 mm. in one hour. Five stool examinations for occult blood were negative. A second barium meal study again showed the pronounced constriction of the pyloric antrum, but the proximal limits of this segment had become more sharply defined.

CASE 2.—E.G., aged 82, had a gastroenterostomy in 1925. Since then he had continued to have episodes of epigastric pain and vomiting. No relevant abnormalities were found on physical examination. Hæmoglobin level, white blood cell count and sedimentation rate were normal, and three stool examinations for occult blood were negative. A barium meal study (Fig. 2) in January 1956 showed a well-functioning

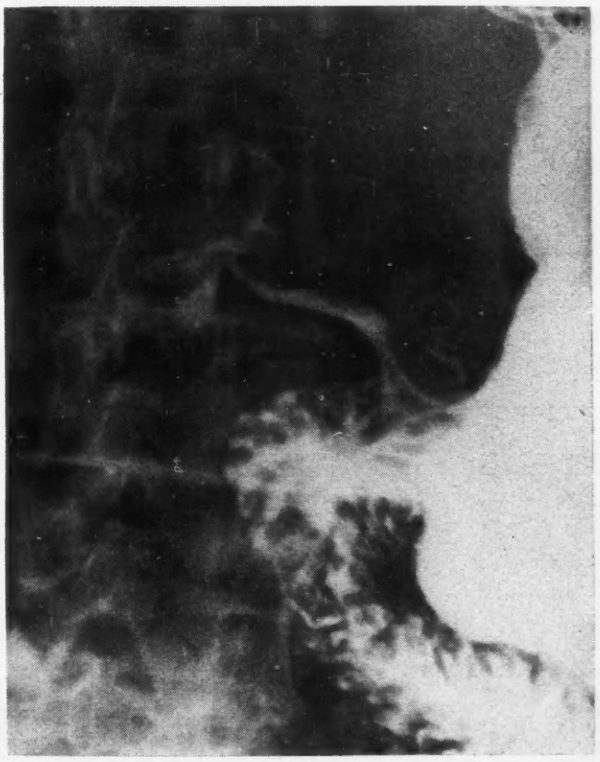

Fig. 1.—Case 1. Marked contraction of the pyloric segment "suggesting scirrhous carcinoma".

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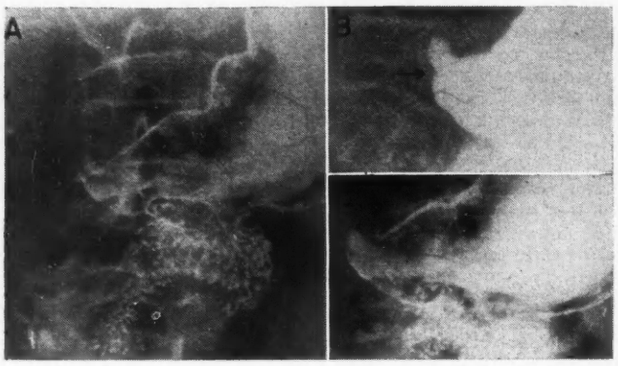

Fig. 2.—Case 2. A. Well-functioning gastroenterostomy. Pyloric segment (arrow) narrowed. B. Attempts to fully distend the pyloric segment with barium and to identify the pylorus were unsuccessful. C. The deformity of the pyloric segment is not a constant one.

gastroenterostomy and narrowing of the segment immediately proximal to the pylorus. Sufficient barium could not be passed through this region to identify the pylorus clearly. At gastroscopy, the posterior gastroenterostomy stoma appeared normal. No angulus was seen. The pyloric segment was narrowed. The pylorus, which appeared atrophic, was seen to contract. Over a small area proximal to the pylorus the mucosal folds were large, œdematous and hyperæmic, and mucus was abundant. Elsewhere the mucosa appeared normal. He died in March 1957, of unrelated causes. At autopsy it was reported that the stomach was contracted and that the gastric mucosa appeared atrophic. No evidence of gastric carcinoma or ulceration was found. It was unfortunate that no special attention was paid to the pyloric segment.

CASE 3.—W.M., aged 74, had a gastroenterostomy in May 1951, because of pyloric obstruction due to duodenal ulcer disease. In August 1955, he had jaundice, and diagnoses of Lænnec's cirrhosis and biliary tract calculus disease were established. Occult blood in the stools varied from none to 4-plus. A barium meal study (Fig. 3) showed a well-functioning gastroenterostomy. The pyloric portion of the stomach appeared to be shortened and narrowed, with a suggestion of thickening of the wall and loss of mucosal markings. It was difficult to identify the pyloro-duodenal junction. At gastroscopy a contracting pylorus was seen. The pyloric segment was possibly smaller than normal but it was not contracted as in Cases 1 and 2. The mucosa appeared normal. The jaundice subsided, and no operation was performed. In August 1957, he

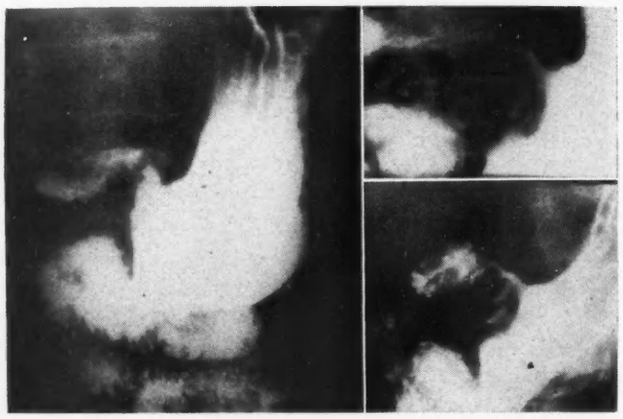

Fig. 3.—Case 3. Illustrates shortening and narrowing of the pyloric segment with difficulty in defining the gastro-duodenal junction.

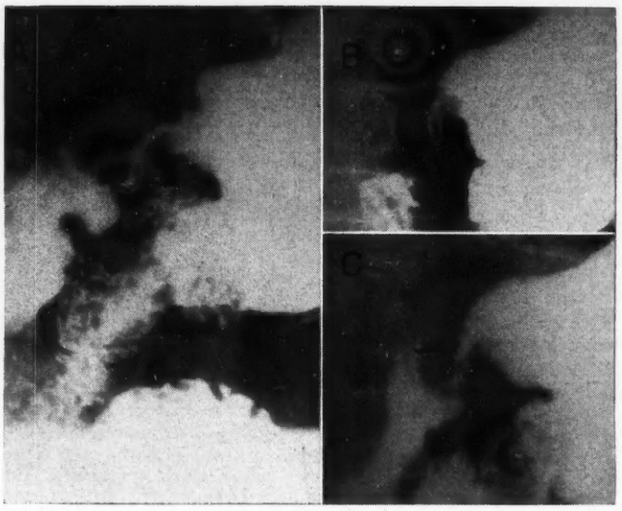

Fig. 4.—Case 4. A. Pyloric segment of stomach shortened, narrowed and poorly filled. B. More filling of pyloric segment proximal to tubular area of narrowing. C. Showing duodenum well filled while pyloric area remains constricted.

complained of minimal epigastric discomfort. His appetite was good and his weight well maintained. He looked well. Hæmoglobin level, white blood cell count and sedimentation rate were normal. A barium meal study showed no significant change from the examination done two years earlier. In June 1958, he was admitted to hospital for investigation of headaches, for which no organic cause was found. There were no gastro-intestinal complaints.

CASE 4.—E.F., aged 78, had a gastroenterostomy in 1933 because of persistent vomiting. He was admitted to Shaughnessy Hospital in September 1953, because of weakness and tarry stools. A barium meal study (Fig. 4) showed that the pyloric segment of the stomach distal to the gastroenterostomy was narrowed and could not be well filled. At gastroscopy the stoma appeared normal. Only a fair view of the pyloric region was obtained. No abnormalities were visualized. In August 1957, he had no gastro-intestinal complaints. He looked well and there were no relevant abnor-

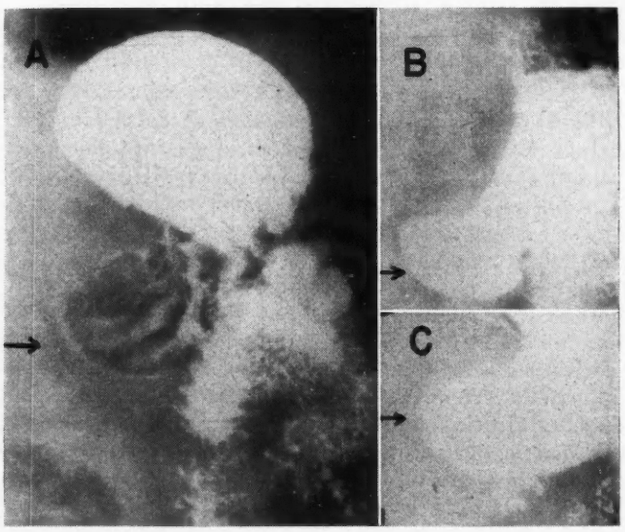

Fig. 5.—Case 5. A and B. Stomach distal to gastroenterostomy outlined by air. No barium entered the pyloric canal and the duodenum could not be demonstrated. (Two round collections of barium are seen to the left of the stoma.) C. No change in pyloric area despite more distension of this area with barium.

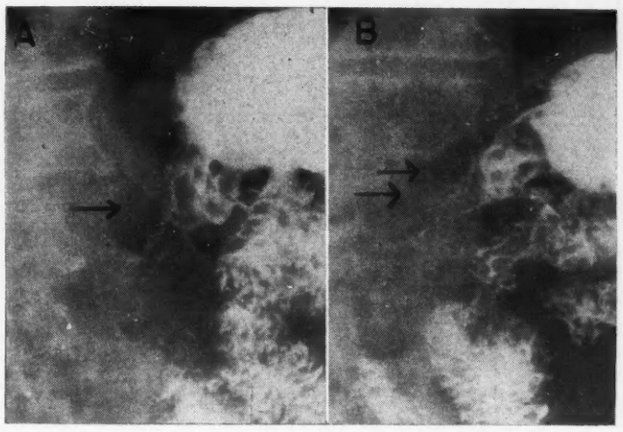

Fig. 6.—Case 6. Alteration of mucosal pattern of pyloric antrum strongly suggestive of scirrhous carcinoma. Tubular narrowing of distal pylorus with constant deformity.

malities on examination. A second barium meal study showed no change in the pyloric segment.

CASE 5.—W.R., aged 80, had a gastroenterostomy in 1917. Since then he had had occasional lower abdominal pain and constipation. In March 1956, there were no relevant physical findings. Two stool specimens for occult blood were negative and one was positive. A barium study (Fig. 5) showed a well-functioning gastroenterostomy but no barium entered the pyloric canal and the duodenum could not be demonstrated. Barium was present in round collections to the left of the stoma. At gastroscopy the posterior gastrojejunostomy appeared normal. The angulus was very prominent. The pyloric antrum was small and conical and the mucosa showed no abnormalities. The pylorus was visualized. Three orifices were seen near the angulus and it was considered that these probably represented openings of fistulæ. In August 1957, he was well except for recently developed thrombophlebitis of one leg. Hæmoglobin level, white blood cell count and sedimentation rate were normal. A second barium meal study showed no change.

CASE 6.—G.G., aged 65, had had abdominal operations in 1927 and in 1949. It could not be established at which of these a gastroenterostomy had been performed. In January 1956, he complained of a weight loss of 10 lb., anorexia and epigastric pain (relieved by baking soda) of three months' duration. Examination revealed no relevant findings, and three stool specimens were free of occult blood. A barium meal study (Fig. 6) showed a functioning gastroenterostomy. The pyloric antrum "appeared markedly narrowed and there was an alteration in the mucosal pattern of the antrum strongly suggestive of scirrhous carcinoma." At gastroscopy the gastroenterostomy stoma appeared normal. The pyloric segment was markedly narrowed and its mucosa appeared normal. The pylorus was not seen. There was no evidence of carcinoma or gastritis. However, because the pylorus was not seen, one could not be sure of the limits of the pyloric segment. In October 1957, he complained only of minimal epigastric distress. He looked well, had not lost weight and presented no abnormalities on physical examination. Hæmoglobin level, white blood cell count and sedimentation rate were normal. A second barium meal showed no change.

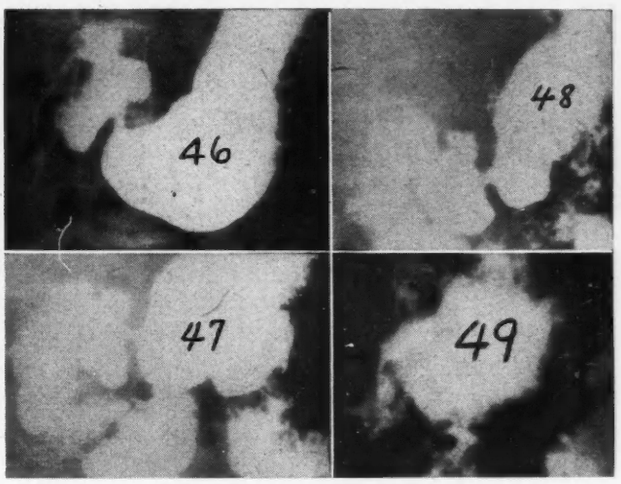

Fig. 7.—Case 7. Duodenal deformity due to ulceration before gastroenterostomy (46). Studies performed in 1947 (47) and in 1948 (48) show normal pyloric segment. Narrowing of pyloric segment was seen in 1949 (49).

CASE 7.—A.D., a 69-year-old physician, had had epigastric pain, nausea and occasional vomiting for 18 years, due to duodenal ulcer disease. A vagotomy and posterior gastroenterostomy were performed in 1946. Fig. 7 (46) shows the duodenal deformity preoperatively. Subsequent films in 1947 and 1948 showed a normal pyloric segment, but by 1949 its diameter had diminished (arrow). By 1950 (Fig. 8A, B, and C) further narrowing had occurred and by 1952 (Fig. 9) the pyloric segment was a narrow, rigid cone which could be filled with barium only with difficulty. Hæmoglobin level, white blood cell count and sedimentation rate were normal. A diagnosis of cancer was suspected. He was well in 1959, at least nine years after contracture of the pyloric segment was first recognized.

DISCUSSION

The cases described illustrate the condition of benign contracture of the pyloric segment after gastroenterostomy. In most of the patients this radiological configuration was first recognized many years after the operation (Table I). In case 7, contracture of the pyloric segment was first ob-

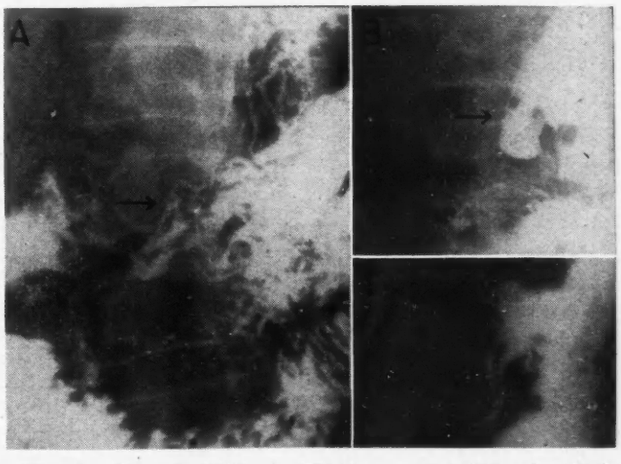

Fig. 8.—Case 7, 1950. A. Further narrowing of pyloric segment. B. Showing incomplete filling of distal pyloric segment. C. Distal pyloric segment fills as a narrow tubular structure.

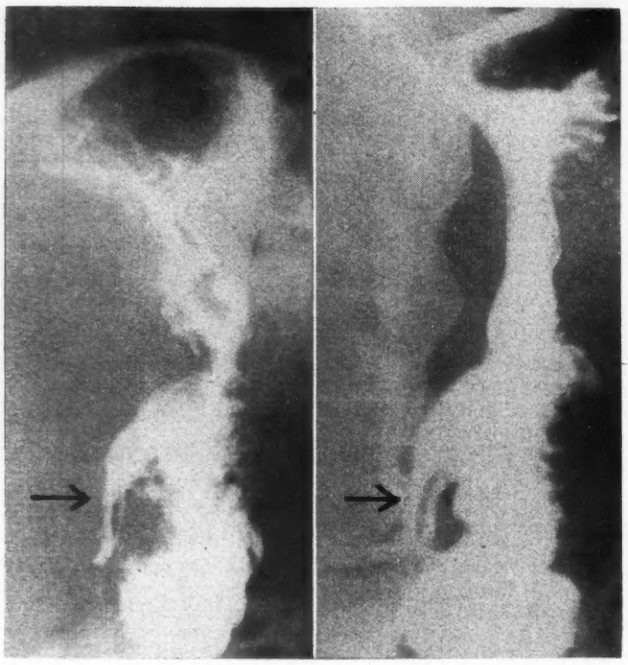

Fig. 9.—Case 7, 1952. Pyloric segment has become a narrow rigid cone which is filled with difficulty.

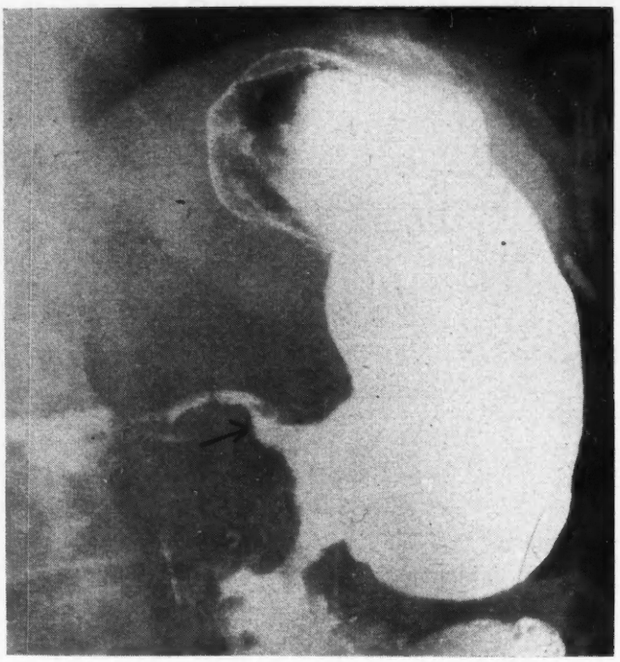

Fig. 10.—Case 8. Illustrates marked narrowing of the pyloric antrum due to carcinoma in a 65-year-old woman. A gastroenterostomy performed 30 years earlier continues to function.

served three years after operation and became more pronounced in subsequent years. Gastroscopy was performed on all but one patient (No. 7). The follow-up period varied from 13 months to nine years. During this period none has developed clinical evidence of carcinoma of the stomach.

The chief problem in the management of these patients has been to exclude carcinoma of the pyloric segment. Carcinoma was frequently suggested by the radiologist. Although this complication was previously considered uncommon after gastroenterostomy, recent observations[1] suggest that gastroenterostomy has no effect on the subsequent development of carcinoma. That the deformity described is not invariably innocent is illustrated by the following case in which the radiological configuration was erroneously considered to be due to benign deformity.

TABLE I.—PATIENTS WITH BENIGN CONTRACTURE OF THE PYLORIC SEGMENT AFTER GASTROENTEROSTOMY

Case No.	*Age*	*Interval from gastro-enterostomy until condition found*	*Observation time after diagnosis*	*Gastroscopy*	*Clinical state*
1. R.L.	68	38 years	16 months	Yes	Well
2. E.G.	82	29 years	13 months	Yes	Dead
3. W.M.	74	4 years	34 months	Yes	Well
4. E.F.	78	20 years	46 months	Yes	Well
5. W.R.	80	39 years	17 months	Yes	Well
6. G.G.	65	29 years	19 months	Yes	Well
7. A.D.	69	3 years	9 years	No	Well

CASE 8.—This 65-year-old woman had had a gastroenterostomy performed about 1926 because of pyloric obstruction due to duodenal ulcer disease. In October 1956, she was seen because of periodic vomiting and epigastric pain relieved by alkalis. This was followed later by a weight loss of about 40 lb. in about four weeks. A barium meal (Fig. 10) showed a well-functioning gastroenterostomy. The pyloric antrum was markedly constricted and constantly deformed, with a lumen measuring no more than one centimetre. The radiological configuration was similar to that seen in patients with the benign deformity described above. An attempt to carry out gastroscopy was discontinued because of peripheral vascular collapse. At laparotomy four months later a large hard mass was found involving the distal third of the stomach. Histologically this was a colloid adenocarcinoma.

Little has been written of the benign contracture of the pyloric segment that may occur after gastroenterostomy. It has been briefly described by British radiologists[2] who have attributed it to spasm, interstitial fibrosis and epigastric adhesions and have recognized the difficulty in distinguishing it from carcinoma. In an exhaustive review of the radiological abnormalities of the pyloric antrum, Jenkinson[3] does not mention this condition. In a review of 825 patients with gastroenterostomies subsequently operated upon,[4] no comment was made regarding contracture of the pyloric antrum. It is of interest that 13 of these 825 patients were found to have carcinoma of the stomach.

The deformity as seen radiologically consists of varying degrees of cone-like narrowing of the pyloric antrum. The antrum may also appear shortened. Attempts to distend it fully with barium are usually unsuccessful. The deformity is usually constant but at times some variation in its configu-

ration, particularly of the proximal portion, may be seen. It is usually difficult or impossible to demonstrate the pyloro-duodenal junction. The mucosa of the deformed area usually presents a smooth appearance. The cause of this radiological configuration of the pyloric segment is uncertain. In some patients with gastroenterostomies the radiologist may experience difficulty in filling the pyloric segment. However, incomplete filling or spasm can hardly be the cause of a usually constant or progressively increasing deformity (Figs. 7, 8 and 9). The possibility that the deformity is related to postoperative adhesions is unlikely, since contracture occurs only distal to the gastroenterostomy. The occurrence of a gastric ulcer which subsequently heals, resulting in scar formation, may be considered as a possible cause of such a deformity, but a gastric ulcer has not been demonstrated in any of the cases described. That the deformity is due to antral gastritis, possibly associated with reflux of intestinal juices through the gastroenterostomy stoma, is unlikely, since only one of the six patients on whom gastroscopy was performed showed evidence of antral gastritis. Antral gastritis itself may enter into the differential diagnosis, however. Irradiation fibrosis due to repeated use of diagnostic radiological studies is a possible but very unlikely cause. It is considered more likely that the muscle of the pyloric segment undergoes disuse atrophy followed by fibrosis and contracture. Histological observations will be required to ascertain the precise nature of this deformity.

This condition is of some clinical importance because it may be confused with carcinoma. Careful consideration of the history, physical findings and laboratory data may be important aids in differentiating these conditions. Radiologically, a smooth conical narrowing of the pyloric antrum without a filling defect favours the diagnosis of benign pyloric segment contracture. Short of surgical exploration, gastroscopy appears to be the most conclusive examination. Visualization of the pylorus and a normal mucosa in the conical contracted segment argues strongly in favour of benign contracture. Inability to visualize the pylorus makes it impossible to define the limits of the pyloric segment. The possibility of carcinomatous infiltration without mucosal involvement is another limiting factor to accurate diagnosis by gastroscopy. It is also important to note that observation of a sphincter-like closure of the pylorus does not with certainty exclude a lesion of the pyloric ring.

SUMMARY

The findings in seven patients with benign contracture of the pyloric segment occurring after gastroenterostomy for peptic ulcer disease are described. In most of these patients this complication was noted several years after operation. The radiological configuration may be confused with carcinoma of the stomach. Short of surgical exploration, gastroscopic examination is the most reliable method of establishing the correct diagnosis. This condition does not appear to have been described in detail previously.

The authors gratefully acknowledge the co-operation of Dr. M. R. Dickey, Dr. W. R. Woodley, Dr. A. D. McKenzie, Dr. J. W. Wilson and Dr. H. R. Robertson.

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RÉSUMÉ

On a découvert une contracture bénigne de la portion pylorique se produisant après gastro-entérostomie pour ulcère peptique chez sept malades dont on donne les faits cliniques dans le texte. Cette complication n'est survenue que plusieurs années après l'opération. On tente de l'expliquer par une atrophie de cessation de l'usage suivi de fibrose et de contractures. L'apparence radiologique peut porter à confusion avec le cancer d'estomac. A part l'exploration chirurgicale, l'examen gastroscopique est la méthode la plus sûre d'établir correctement le diagnostic. Cet état ne semble jamais avoir été décrit auparavant.

TRIFLUOPERAZINE IN PSYCHONEUROTIC OUTPATIENTS

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REPORTS ON trifluoperazine (Stelazine) to date have dealt principally with its use in hospitalized psychotic patients. In general, they indicate that the drug, besides controlling excessive psychomotor agitation, often exhibits stimulant properties that could be used to advantage in treating withdrawn patients as well as chronic psychotics, resistant to other forms of drug therapy. Brooks[1] and Kovitz,[2] working separately, reported that trifluoperazine often motivated sedentary, uncommunicative patients. Their observations complemented clinically the interesting studies of Lehmann and Knight,[3] who administered a series of preclinical psychophysiological tests to determine as exactly as possible the effects of trifluoperazine. Results of these tests indicated that the drug increased attention, concentration and general vigilance. Studies in animals demonstrated the relative safety of trifluoperazine.[4] Subsequent clinical studies have uncovered no evidence of jaundice, blood dyscrasias, seizures, or significant hypotension associated with its use.[5, 6]

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Canad. M. A. J.
Sept. 15, 1959, vol. 81

Our own experience with trifluoperazine began in March 1958. At that time we began using the drug in a small group of non-psychotic patients seen in the psychiatric unit and on the outpatient service at Victoria Hospital. These initial trials were promising and the drug was well received by the patients. After the drug had been used in a variety of emotional disturbances, it was possible to come to some preliminary conclusions; namely, that trifluoperazine appeared to be especially helpful in treating both chronic and acute anxiety, and that it apparently had little effect on patients with agitated depressions or obsessive compulsive reactions. This report summarizes our experience with the drug and points up the special usefulness of trifluoperazine in the psychoneurotic outpatient.

SELECTION OF PATIENTS

In the course of this evaluation, 72 psychoneurotic outpatients (50 women and 22 men) were given trifluoperazine. Their ages ranged from 14 to 68 years; the majority were between 20 and 40. Approximately 75% of these patients had been referred to the psychiatric service by general practitioners or internists on the hospital staff who had already ruled out organic disease as the cause of the patients' symptoms. In the remainder of the patients—most of whom had come on the recommendation of clinics or other patients' services familiar with our outpatient psychiatric clinic—physical examinations and laboratory studies were ordered to detect possible organic disease whenever indicated.

Generally speaking, these psychoneurotics presented a picture of discomfort and weariness, of being pressed to the edge of panic by their worries and vague fears. Their complaints included irritability, insomnia, wide swings in mood, inability to concentrate, and anorexia. Some emphasized physical complaints such as headaches, dizziness, palpitations, hyperventilation, nausea, or epigastric distress. Their anxiety rendered them unable to cope with everyday environmental situations and responsibilities. The diagnoses of the patients are listed in Table I.

TABLE I.—RESULTS IN RELATION TO DIAGNOSES

Diagnoses	*No. of patients*	*Results*			
		Excellent	*Good*	*Fair*	*Poor*
Involutional melancholia.	2	1	1		
Chronic anxiety	38	28	7	2	1
Acute anxiety	13	11	1	1	
Schizo-affective illness with anxiety	3	1		1	1
Acute anxiety with depression	4	4			
Chronic anxiety with depression	4	2	2		
Involutional reactions	4	4			
Agitated depression	1			1	
Conversion hysteria	1	1			
Manic-dep. depression	1		1		
Obsessive compulsive	1				1
Totals	72	52	12	5	3

For the most part, patients chosen were those with illnesses of long standing who had not shown a satisfactory response to the ataractic drugs. As Table II shows, 31 of the patients had been ill for over five years and 29 had been ill for a period of from one to five years. Twelve patients had become ill during the preceding 12 months. Fifty-seven of the 72 patients had not responded or had responded inadequately to previous ataractic drugs or sedatives, singly or in combination, including promazine, chlorpromazine, prochlorperazine, meprobamate, and azacyclonol. Fifteen patients had received no previous drug therapy.

METHOD

The usual starting dosage of trifluoperazine was 1 or 2 mg. three or four times daily, depending on the intensity of the patient's symptoms. Dosage was subsequently adjusted according to patient response. In most cases, it was possible to reduce dosage to 1 mg. twice daily within one to two weeks. Patients were seen weekly at first and then every two weeks for interview and adjustment of dosage as needed. The average duration of therapy was four weeks, although some were treated for as long as eight weeks.

RESULTS

The results of trifluoperazine therapy in relation to diagnoses are presented in Table I; Table II shows results in relation to length of illness. Fifty-two of the 72 patients treated became symptom-free, were able to return to employment or normal responsibilities, and were better able to adjust to stressful situations. They felt no further need to take the drug. Twelve patients reported that their symptoms were well controlled and that they felt comfortable, but needed occasional help from the medication during periods of stress. In eight patients the treatment was considered a failure, even though five showed partial improvement in some symptoms; the other three did not benefit from the drug.

TABLE II.—RESULTS IN RELATION TO DURATION OF ILLNESS

	Results				
	Excellent	*Good*	*Fair*	*Poor*	*Total*
Over 5 years	14	9	5	3	31
1 to 5 years	27	2	—	—	29
Less than 1 year	11	1	—	—	12
Totals	52	12	5	3	72

The fact that a majority of these patients voluntarily discontinued the medication and continued to feel well seems noteworthy. With some ataractic drugs it has been our experience that a number of psychoneurotic patients improve only while taking the drug and are therefore reluctant to discontinue it.

The results according to length of illness (Table II) indicate that trifluoperazine is effective not only in short-term illnesses, which usually respond well to any therapy, but also in emotional disorders of long standing which generally have a less favourable prognosis.

Trifluoperazine appeared to have a rapid onset of action; patients reported that they often noticed some improvement within the first day or two on the medication. It was usually possible to tell by the second week of therapy whether the drug was going to prove effective. By the second visit, patients who were benefiting from the drug generally said that they felt less irritable and worried, and that their eating and sleeping had improved.

Somatic complaints subsided too, as the drug relieved tension and helped promote patient-physician rapport. With supportive psychotherapy to reinforce these gains from trifluoperazine, patients became able to function more comfortably in environmental situations that they had previously retreated from or rebelled against. In time, their vague fears, conflicts and resentments became less and less important to them. Those whose anxiety had made them indecisive, confused, and unable to concentrate reported a return of their former efficiency in performing daily tasks. In some patients, such as those with chronic fatigue in spite of inactivity, the drug seemed to have a desirable stimulant effect; it appeared to make communication and personal contacts easier for withdrawn patients who had experienced fear and difficulty in such situations.

As had been indicated in our preliminary trials, the drug was most effective in relieving anxiety, chronic as well as acute. Typical of the favourable response seen in chronic patients was that of a young girl in her twenties who had been under psychiatric care for eight years and had been in the hospital six times in the last four years. This extremely neurotic young woman is the product of a stress-laden environmental situation: her father is a reformed alcoholic turned religious fanatic and her mother a psychoneurotic personality. Unable to cope with her home situation, the girl developed pain in her throat and dysphonia. After numerous negative physical examinations and studies, she was referred for psychiatric care. She has responded well to counselling in conjunction with trifluoperazine and is now back at work for the first time in four years. Her complaints disappeared as her anxiety and tension lessened.

As can be seen from Table I, trifluoperazine was of less value in treating obsessive compulsive reactions, agitated depressions, or schizo-affective types with anxiety. These patients were early in the series and helped delineate the indications in which the drug might be expected to prove useful. Some attempt was made to combine trifluoperazine with electroshock therapy; results were unsatisfactory. Two neurotic depressives who were treated in this manner became confused and disoriented. It was necessary to discontinue the drug for a week before continuing electroshock therapy; no further trouble occurred when therapy was resumed.

Side Effects

In all, nine patients reported side effects. Three complained of severe headaches which subsided when the dosage was reduced from 1 mg. four times daily to 1 mg. twice daily without compromising therapeutic gains. Six patients mentioned drowsiness, which did not seem unusual at first since drowsiness is a common complaint with ataractic agents. Later, however, when several patients who had to drive as much as 100 miles to and from the hospital were questioned about drowsiness they reported that trifluoperazine did not impair their co-ordination, reflexes or judgment. None said that they had difficulty in staying awake or remaining alert, even though some were on a dosage of 2 mg., four times daily. In spite of their drowsiness, several mentioned that they did not fall asleep when they lay down for a nap during the daytime. Thereafter, when patients mentioned drowsiness I inquired further and concluded that what many were calling drowsiness was simply relaxation, an unfamiliar feeling to these tense people.

Weight gain from 10 to 20 lb. was noted in six patients receiving trifluoperazine. All had been underweight and unable to eat because of their tension. For example, a young woman who was "unable to face food" and weighed only 72 lb. gained 18 lb. during four weeks' treatment with trifluoperazine, instituted to relieve her symptoms. In all likelihood, weight gain in these patients came from diminished tension rather than any specific effect of trifluoperazine.

No evidence of extrapyramidal symptoms was observed in these patients. No incidents of hypotension, jaundice or blood dyscrasias occurred.

Summary

Seventy-two psychoneurotic outpatients were treated with trifluoperazine, a phenothiazine derivative. Fifty-two patients became symptom-free and were able to return to employment or resume normal responsibilities; 12 others reported definite improvement and became more comfortable in their environment. Results were considered unsatisfactory in the remaining eight patients, although five of these showed slight improvement in some symptoms. Best results were seen in the treatment of both acute and chronic anxiety. Results were not encouraging in treating obsessive compulsive types, those with agitated depressions, or schizo-affective types with anxiety. Combining trifluoperazine with electroshock therapy caused confusion and disorientation in two patients.

Weight gain was noted in six patients who had been underweight as a result of tension and anorexia. Three patients reported severe headaches which disappeared when dosage was reduced. Drowsiness was not a problem; patients reported no difficulty in remaining alert while driving or carrying on business activities. No evidence of extrapyramidal symptoms, hypotension, jaundice or blood dyscrasias was observed.

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RÉSUMÉ

On a administré du trifluoperazine à 72 psychonévrosés traités à la clinique externe; 52 devinrent asymptomatiques et purent reprendre leur travail et leurs responsabilités; 12 autres montrèrent une amélioration et semblèrent s'adapter à leur milieu. Les résultats chez les huit autres furent considérés comme des échecs bien que cinq d'entre eux obtinrent une légère amélioration de l'un ou l'autre de leurs symptômes. Les meilleurs résultats sont obtenus dans le traitement de l'angoisse aiguë ou chronique. Les résultats dans le traitement des obsessifs, des déprimés agités ou des angoissés schizo-affectifs ne sont pas brillants. La combinaison trifluoperazine-sismothérapie produisit de la confusion et de la désorientation chez deux malades. Six malades dont la tension nerveuse avait déprimé l'appétit gagnèrent du poids au cours du traitement. Trois malades accusant des céphalées graves les perdirent après que la dose fut diminuée. L'assoupissement ne présenta aucun problème, les malades n'eurent pas de difficulté à rester éveillés au volant de leur voiture ou à vaquer à leurs occupations. On n'observa aucun signe d'atteintes extra-pyramidales, d'hypotension, de jaunisse ou de trouble de la crase sanguine.

SUSTAINED RELEASE OF DRUGS IN CERTAIN DRUG-RESIN COMPLEXES AS JUDGED BY URINARY EXCRETION RATES*

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IN RECENT YEARS, ever increasing numbers of drugs have appeared on the market in forms claimed to provide for sustained release of the particular drug. One technique which has been used to provide this effect is creation of a complex of the drug with a suitable ion exchange resin. It is claimed that upon contact with the gastric and intestinal juices the drug is released at a uniform rate for a prolonged period of time. It is stated[1] that the release of the active principle is controlled by "the normal laws governing velocity of chemical reactions and is unaffected by enzyme action, peristalsis or other physiological processes".

Chaudhry and Saunders[2] showed that creating a complex of ephedrine with sulfonic acid cation exchange resins resulted in release of the drug *in vitro* over a period of more than six hours. Clinical trials[3] of this preparation indicated reduced incidence of asthma attacks over 10-12 hours, and appeared to substantiate the *in vitro* results. Abrahams and Linnell[1] found that after the ingestion of pure creatinine a peak blood level was obtained in two hours, falling rapidly to normal in about eight hours. When creatinine resinate was given, however, it was reported that absorption was delayed and a high blood creatinine level sustained over a much longer period. Urinary excretion appeared to parallel blood levels.[3] An amphetamine resinate preparation was reported to inhibit appetite effectively over a period of 12 hours. Using another resin-amphetamine complex, Freed, Keating and Hays[4] concluded, as a result of clinical tests, that the drug was released *in vivo* on a predictable basis for a period of 10-14 hours.

The value of urinary excretion as a measure of physiological availability of medicaments in coated and uncoated tablets has been demonstrated in this laboratory, and its possible application to timed disintegration or sustained release preparations suggested.[5, 6] Swintosky *et al.*[7-10] studied in detail the kinetics of the absorption, distribution and excretion of sulfaethylthiadiazole and outlined the mathematics of these processes. They showed that many drugs are eliminated from the body at a first order rate and that the half-life of a drug ($t\ ½$) may be calculated from rate of disappearance in either blood or urine. Their work thus substantiated the suggested use of urinary excretion as a possible criterion for the evaluation of timed release or sustained release medication. Nelson[11] outlined the mathematics of sustained release of products given orally, and appears to have been the first to attempt to place the evaluation of these preparations on a sound scientific basis. Blythe[12] discussed the relative merits of different methods of testing these preparations. More recently Campbell, Nelson and Chapman[13] have proposed criteria for the evaluation of sustained release of drugs using the urinary excretion technique.

It is the purpose of this paper to compare rates of excretion in the urine of human subjects following the ingestion of the resinates with those of the pure drugs, and further to relate excretion rates of amphetamine resinates *in vivo* to release rates *in vitro*.

EXPERIMENTAL

Three drugs—creatinine, acetylsalicylic acid and amphetamine sulfate—were used in these studies. Twelve males ranging in age from 29 to 44 years

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TABLE I.—TWENTY-FOUR HOUR EXCRETION OF CREATININE FOLLOWING INGESTION OF NO DOSE, 1000 MG. IN SOLUTION AND 3.33 GRAMS OF RESINATE (EQUIVALENT TO 1000 MG. CREATININE).*

	Blanks		*Creatinine solution*			*Creatinine resinate*		
						Lot A		*Lot B*
Subject	*Test 1* mg.	*Test 2* mg.	*Test 1* mg.	*Test 2* mg.	*Repeat dose* mg.	*Test 1* mg.	*Test 2* mg.	*Test 1* mg.
A	1768	1757	980	802	975	718	536	578
B	1777	—	—	1154	1161	—	943	—
C	1835	1787	1176	756	827	944	—	—
D	1602	1732	956	856	826	721	767	504
E	1804	1711	912	800	844	750	927	974
F	1532	1715	847	1041	874	590	784	772
G	2091	2023	968	1034	922	733	610	584
H	1898	1744	900	810	732	758	721	560
I	1742	—	814	—	—	668	—	—
J	1720	—	965	—	—	755	—	—
K	—	—	—	—	734	—	—	—
L	—	—	—	—	1055	—	—	—
Mean	1777	1781	946	907	895	737	755	662
S.D.	±154	±110	±103	±147	±137	±94	±151	±189
Mean per cent of dose	—	—	95	91	90	74	76	66
Availability (per cent)	—	—	—	—	97	80	81	71

*Net excretion where dose was given.

volunteered to act as subjects. All were given physical examinations and found to be medically fit.

For each drug, data were obtained on the blank urinary excretion for each individual for 24 to 56 hours before the ingestion of the drug, for 24 to 56 hours after the ingestion of the pure drug taken in solution (acetylsalicylic acid was taken in the form of a rapidly disintegrating compressed tablet), and for the same period of time after ingestion of the drug-resin complex. All tests were begun at 8.45 a.m. Drug determinations were made on urine samples collected at most or all of the following times: 2, 4, 6, 8, 10, 12, 14.5, 24, 28, 32, 38.5, 48, 52 and 56 hour periods from the start of the test until excretion levels reached those on blank urine samples. The use of blank determinations corrected for any lack of specificity of methods or endogenous excretion.

Creatinine was determined by the Jaffe reaction,[14] acetylsalicylic acid by the ferric nitrate reaction[15, 16] and amphetamine by the methyl orange reaction.[17-19] All resulting colours were read in an Evelyn colorimeter at the appropriate wavelength. For convenience the method used for the determination of amphetamine is given below.

DETERMINATION OF AMPHETAMINE

Reagents

1. Chloroform.

2. Methyl orange solution. Add 500 mg. methyl orange to 100 ml. water at about 40° C. Shake occasionally for about 20 min. Cool and filter.

3. Boric acid solution. Saturated solution of boric acid.

4. Borate buffer. Use sodium borate for preparing 0.2M saturated solution. The pH of this solution is between 9.8 and 10. Do not refrigerate.

5. Acidified alcohol. Add 2 ml. conc. H_2SO_4 to 100 ml. of absolute alcohol. Keep stoppered to prevent solution taking up moisture.

6. Standard amphetamine solution. Dissolve 50 mg. of pure *dl*-amphetamine or dextro-amphetamine sulfate in distilled water and make to 100 ml. with distilled water. Store in refrigerator. Prepare working standard by diluting 2 ml. of the stock solution to 100 ml. with 0.1 N H_2SO_4. Store in refrigerator. One ml. of this solution is equivalent to 10 μg. *dl*-amphetamine sulfate or dextro-amphetamine sulfate.

7. NaOH solution 2.5 N. Dissolve 10 g. of NaOH in distilled water and make up to 100 ml. with distilled water.

8. Methyl orange reagent:

Prepare immediately before use by mixing equal volumes of boric acid solution and methyl orange solution.

Equipment: (1) Centrifuge tubes. (2) Shaking machine and high speed centrifuge.

Standard Curve

Use a concentration of 5 μg. to 40 μg. of amphetamine per tube for the standard curve. Pipette 0.5 ml. of 2.5N NaOH into each of the 40 ml. glass-stoppered centrifuge tubes, followed by the graded amounts, 0, 0.5, 2.0, 3.0 and 4.0 ml. of amphetamine working standard solution. Stopper the tubes and shake for one minute. Make up the volume of each tube to 5.0 ml. with distilled water. Add 5.0 ml. of the buffer solution to each tube. Stopper and again shake the tubes. Add 20 ml. of $CHCl_3$ to each of the tubes, and shake on a "Yankee" Kahn shaker or on any other type of shaker which has about 275 oscillations per minute, for 20 minutes. Centrifuge the tubes until the chloroform layer is perfectly clear. This takes about 20 minutes at a speed of 2000 r.p.m. Carefully pipette 15 ml. of the chloroform layer, free from even a trace of the aqueous phase, to another centrifuge tube containing 0.5 ml. of a fresh solution of methyl orange reagent. Stopper the tubes and shake again for 20 minutes. Centrifuge the tubes until the chloroform layer is perfectly clear. Pipette 10 ml. of clear chloroform solution without entrapping droplets of the aqueous phase into colorimeter tubes containing 1.0 ml. of the alcohol reagent. The alcohol reagent should be added just before the addition of the chloroform phase. Gently shake the contents and

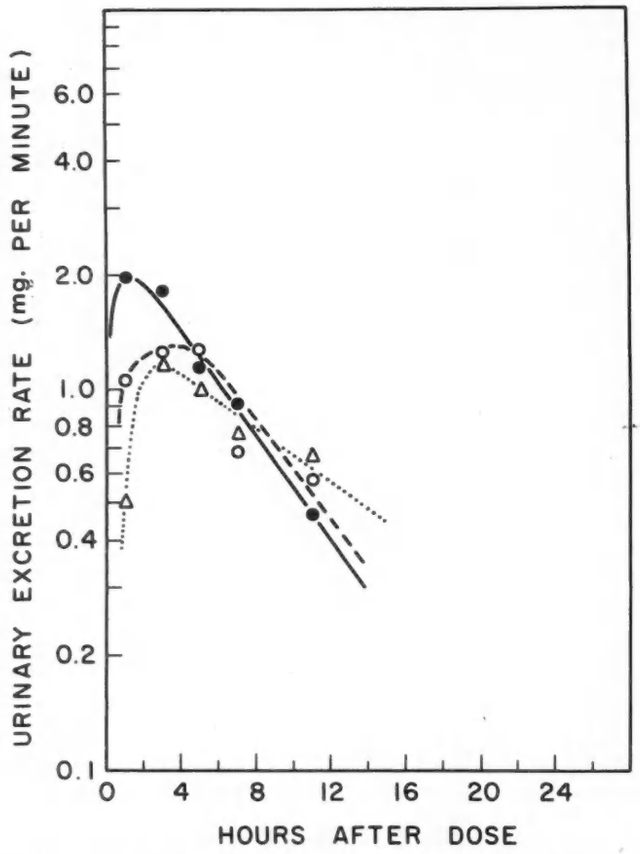

Fig. 1.—Rate of urinary excretion of creatinine. ● —— ● Urinary excretion following ingestion of standard, half-life = 4 hours mean of 2 tests. O - - - O creatinine resinate A, half-life = 4 hours mean of 2 tests. △ ..... △ creatinine resinate B, half-life = 8 hours.

read in the Evelyn photoelectric colorimeter at 515 μ, using the first tube which contains no amphetamine to set the instrument at 100% transmittance. Check the setting after taking each reading.

Urine.—Depending upon concentration of amphetamine in urine, pipette 2 to 3 ml. of urine into centrifuge tubes, add 0.5 ml. of 2.5N NaOH, shake the tubes for one minute, and proceed as described under Standard Curve.

Reproducibility of Method

An intensive study of the amphetamine method indicated that there was a linear relation between absorbance and concentration over a range of 5 to 50 μg. per tube. The mean coefficient of variation of absorbancies at points on the standard curve tested at different times over a period of one year was 4.5%. Mean recovery of known amounts of *d*-amphetamine from urine samples was 97%. No significant change in recovery was found after storage of urine for 24 hours at room temperature or at 5° C. The coefficient of variation of duplicate aliquots of the same urine sample assayed independently was 7%. That the reaction is specific is shown by the fact that 2000 μg. p-hydroxy-amphetamine, a metabolite of amphetamine, is required to give the same absorbance as 5 μg. amphetamine.

RESULTS

Creatinine

In Table I is shown the amount of creatinine ordinarily excreted by each subject over a 24-hour period without dose, with a dose of 1000 mg. pure creatinine and with a dose of 1000 mg. creatinine as the resinate. The figures for the latter two are corrected by subtracting the appropriate blank values. Two lots A and B of creatinine resinate were also tested. Lot A was studied on two occasions and Lot B once. While the coefficient of variation of the blank excretion was less than 10%, it was considerably higher for the resinate.

About 93% of the dose of creatinine in solution was recovered in the urine, while only 66 to 76% of the creatinine was recovered from the resinates. Union with the resin therefore reduced the availability of this drug to 71 to 81%. The mean rates of urinary excretion of creatinine after ingestion of the pure material in solution and the creatinine resinates are shown in Fig. 1. The data on which this and the other figures are based are given in Table II. When plotted on semi-logarithmic paper[11] it was found that the half-life, i.e., time for a given rate of excretion to be reduced to half that rate, was about four hours for both creatinine in solution and for resinate A. There was no evidence of a sustained effect for this resinate. The half-life for resinate B was somewhat longer, suggesting a slight sustained excretion rate. The chief effect shown by both resinates was the lower peak excretion, largely a result of the low avail-

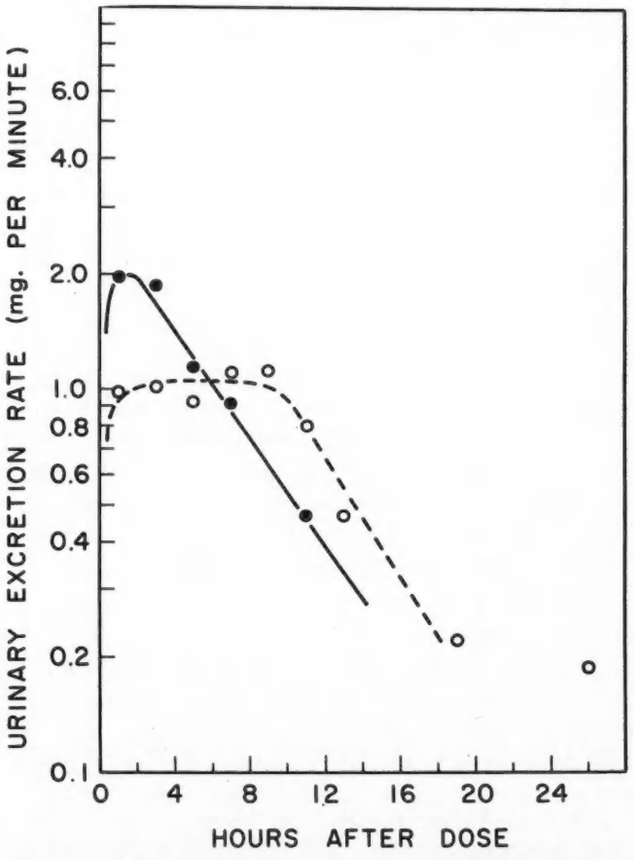

Fig. 2.—Rate of urinary excretion of creatinine. ● —— ● Excretion following ingestion of single dose of 1000 mg. of creatinine in solution. O - - - O Excretion following ingestion of repeat doses of creatinine, 333 mg. at 0 time, 166 mg. at 2, 4, 6 and 8 hr. intervals. In both cases the results are the means of two tests.

TABLE II.—MEAN AMOUNTS OF DRUGS EXCRETED AT VARIOUS INTERVALS

Time after ingestion hours	Creatinine—1000 mg. Standard (solution) test 1 mg.	Standard (solution) test 2 mg.	Resinate Lot A test 1 mg.	Resinate Lot A test 2 mg.	Lot B mg.	Acetylsalicylic acid—972 mg. Repeat dose standard mg.	Standard uncoated tablet mg.	Resinate mg.	Repeat dose standard mg.	Amphetamine—10 mg. Standard (solution) d- test 1 mg.	Standard (solution) d- test 2 mg.	dl- mg.	d- + dl- 48 hour calc'd mg.	Resinate d-form product A mg.	Resinate mixed d- + dl- product B mg.
2	235	237	122	132'	61	118	86	83	50	0.335	0.384	0.317	0.339	0.074	0.205
4	227	207	180	119	143	122	119	120	71	0.563	0.526	0.693	0.619	0.561	0.242
6	154	117	125	183	118	112	132	141	88	0.623	0.683	0.645	0.649	0.550	0.422
8	91	127	85	80	91	132	127	118	91	0.532	0.388	0.744	0.602	0.504	0.370
10	—	—	—	—	—	134	—	—	—	—	—	—	—	—	—
12	—	—	—	—	—	96	—	—	199	—	—	—	—	—	—
14.5	230	138	191	258	270	70	272	222	113	1.045	1.025	1.434	1.235	1.052	1.138
24	9	81	34	−17	−21	70	99	163	162	1.336	0.861	1.061	1.080	1.092	1.197
28	0	0	0	—	—	21	0	0	6	0.162	0.289	0.579	0.403	0.229	0.638
32	—	—	—	—	—	20	0	0	10	0.155	0.179	0.392	0.280	0.010	0.351
38.5	—	—	—	—	—	—	—	—	—	0.043	0.392	0.427	0.323	0.051	0.621
48	—	—	—	—	—	—	—	—	—	0.313	0.476	0.674	0.535	0.598	0.286
52	—	—	—	—	—	—	—	—	—	—	—	−0.014	−0.014	0.013	0.047
56	—	—	—	—	—	—	—	—	—	—	—	0.032	0.032	−0.069	0.038
TOTAL.....	946	907	737	755	662	895	835	847	790	5.107	5.203	6.984	6.083	4.695	5.555
Percent of dose..	95	91	74	76	66	90	86	87	81	51	52	70	61	47	56
Availability (percent)	—	—	80	81	71	97	—	101	95	—	—	—	—	91	91

ability. As shown in Table I, 19 to 29% of the drug was apparently not available to the body.

In order to demonstrate that a sustained excretion effect can be produced with creatinine, 10 subjects were given 333 mg. creatinine in solution at the start of the test at 8.45 a.m. and 167 mg. every two hours thereafter for eight hours, that is, until 1000 mg. had been given. The data shown in Fig. 2 illustrate clearly that there is a uniform rate of excretion which was sustained for about 12 hours. There was no sharp peak to the curve and the overall availability was 97%. There was a marked contrast between the sustained effect in this figure and the slight effect of resinate B in Fig. 1.

Acetylsalicylic Acid

Acetylsalicylic acid was ingested in two forms, as a compressed tablet having an *in vitro* disintegration time of about one minute, and in the form of a resin complex. In both cases, 15 grains or 972 mg. was ingested. The recovery of acetylsalicylic acid in the urine for 24 hours after its ingestion is shown in Table III. The blank excretion of apparent acetylsalicylic acid in the urine is also shown. The availability of acetylsalicylic acid from

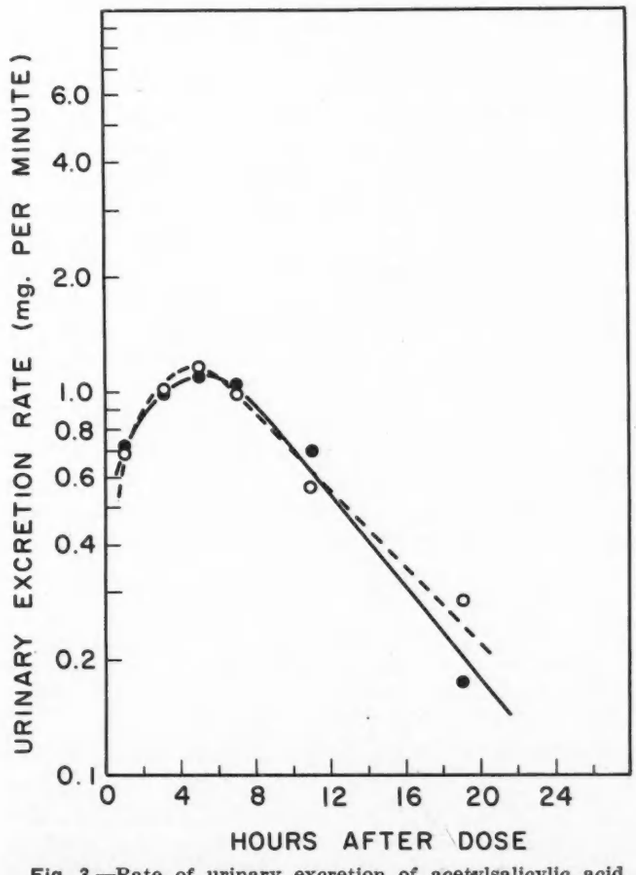

Fig. 3.—Rate of urinary excretion of acetylsalicylic acid. ● —— ● Excretion following ingestion of 15 grains (972 mg.) of acetylsalicylic acid in form of uncoated tablet, half-life 5 hrs. O - - - O Excretion following ingestion of 15 grains in form of resinate, half-life = 6 hrs.

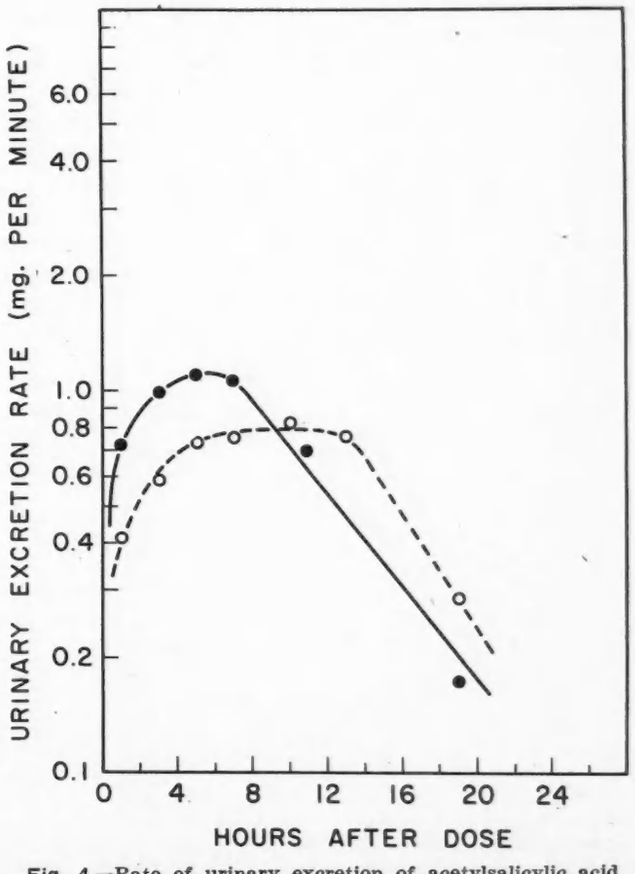

Fig. 4.—Rate of urinary excretion of acetylsalicylic acid. ● —— ● Excretion following ingestion of single dose of 15 grains (972 mg.). O - - - O Excretion following ingestion of repeat doses, 5 grains at 0 time, 2.5 grains at 2, 4, 6 and 8 hr. intervals.

TABLE III.—URINARY EXCRETION OF ACETYLSALICYLIC ACID FOLLOWING INGESTION OF NO DOSE, 972 MG. AS COMPRESSED TABLET AND RESINATE*

Subject	24-hour blanks mg.	Compressed tablet standard mg.	Compressed tablet repeat dose mg.	Resinate mg.
A	213	865	868	824
B	253	—	744	804
C	253	506	739	791
D	211	—	834	—
E	292	868	822	732
F	234	973	—	827
G	255	868	798	954
H	325	893	—	912
K	238	870	725	934
Mean	253	835	790	847
S.D.	±36	±150	±55	±78
Mean percent of dose		86	81	87
Availability (percent)		—	95	101

*Net excretion where dose was given.

the resinate was found to be approximately 100%.

In Fig. 3 is shown the rate of excretion of acetylsalicylic acid for 32 hours after its ingestion. No acetylsalicylic acid was excreted after the 24-hour period from either the compressed tablet or the resinate. The release curves for the two forms of acetylsalicylic acid were very similar, the half-life of the standard being five hours and that of the resinate six hours. There was no evidence of a significant sustained excretion of drug from the complex.

In order to demonstrate sustained excretion with this drug, the effect of repeated doses of a rapidly disintegrating compressed tablet was compared with the standard. Five grains were ingested at 8.45 a.m. and 2.5 grains at 10.45 a.m., 12.45 p.m., 2.45 p.m. and 4.45 p.m. The results are shown in Table III and in Fig. 4. The latter is based on data in Table II. In this case, the peak excretion was absent and there was a region where the rate of excretion was relatively constant and sustained.

Amphetamine

Two commercial amphetamine-resin products were obtained for study. Product A contained dextro-amphetamine sulfate, while Product B contained a mixture of the dextro- and *dl*- forms.

The urinary excretion of apparent amphetamine in the blank urine after ingestion of pure *d*- and *dl*-amphetamine in solution, and after ingestion of the two amphetamine resinates, is shown in Table IV. From 50 to 70% of the amphetamine in solution was excreted, although the variation was rather large. Almost the same amount of amphetamine from both resinates was excreted, the availability being 91%.

The rate of excretion of product A is plotted against time in Fig. 5 along with the standard. The half-life of both the standard and the resinate was found to be about nine hours. The resinate did not exhibit any sustained excretion properties.

The amounts of amphetamine excreted from the mixture of the *d*- and *dl*-forms, shown in Table II and Fig. 6, were calculated from the excretion rates of *d*- and *dl*-forms when ingested separately. The rate of excretion of amphetamine from the resinate containing both *d*- and *dl*-amphetamine is also shown in Fig. 6. The half-life of the resinate in this case was increased more than twofold, from 10 to 23 hours. There was no peak in excretion, and higher rates were maintained from 20 to 36 hours, demonstrating a degree of sustained release.

In vitro Studies

Since Abrahams and Linnell[1] had indicated that a close relationship existed between *in vitro* and *in vivo* rates of release, it was felt that it might be possible to demonstrate differences in the *in vitro* release of the two amphetamine resinates which had shown markedly different *in vivo* excretion rates. An apparatus was designed similar to that used in the replacement closed tube method of Chaudhry and Saunders,[2] in which samples of

TABLE IV.—URINARY EXCRETION OF AMPHETAMINE FOLLOWING INGESTION OF NO DOSE, 10 MG. IN SOLUTION, AND 10 MG. IN FORM OF RESINATES.*

		Standard in solution			Resinates	
Subject	24-hr. blanks mg.	10 mg. test 1 mg.	48-hr. exc. d-form test 2 mg.	56 hr. exc. 10 mg. dl-form mg.	56 hr. exc. from 10 mg. d-form product A mg.	56 hr. exc. from 10 mg. mixed d- and dl-forms product B mg.
A	2.471	5.486	6.870	3.690	6.866	4.955
C	3.756	—	—	9.409	—	6.893
D	3.616	5.377	—	5.830	3.440	3.829
E	2.008	4.715	5.127	3.520	3.022	—
F	3.281	—	—	10.571	5.809	—
G	2.056	4.209	5.093	4.617	3.207	5.837
H	3.480	6.053	—	7.984	4.380	6.165
K	2.969	4.805	3.721	10.249	6.144	5.649
Mean	2.955	5.107	5.203	6.984	4.695	5.555
S.D.	±0.697	±0.657	±1.291	±2.932	±1.567	±1.057
Percent of dose	—	51	52	70	47	56
Availability (percent)	—	—	—	—	91	91

*Net excretion where dose was given.

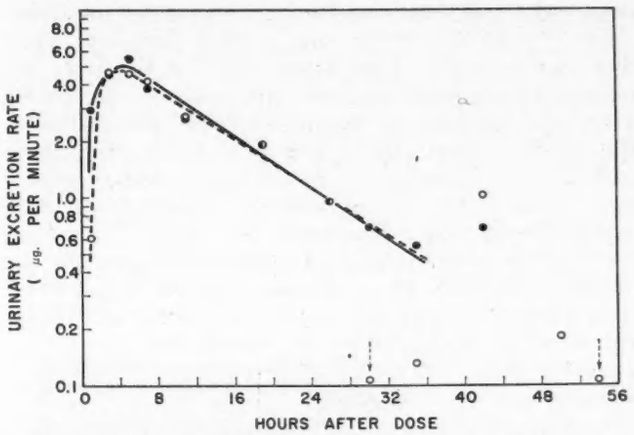

Fig. 5.—Rate of urinary excretion of dextro-amphetamine. ● —— ● Excretion following ingestion of 10 mg. of dextro-amphetamine in solution, half-life = 9 hrs. O - - - O Excretion following ingestion of 10 mg. of dextro-amphetamine (Product A) in form of resinate, half-life = 9 hrs.

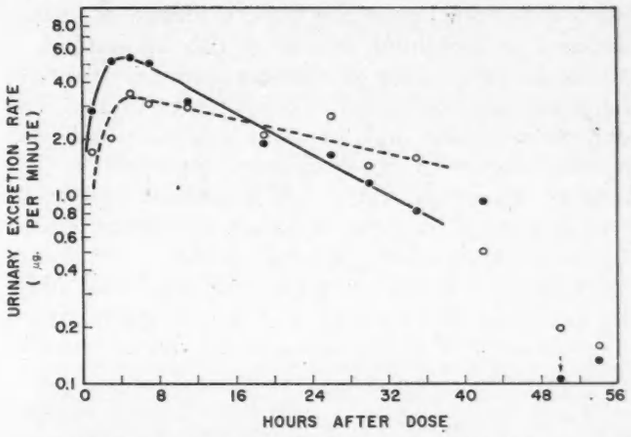

Fig. 6.—Rate of urinary excretion of amphetamine. ● —— ● Calculated excretion following ingestion of 10 mg. of a mixture of equal amounts of *d*- and *dl*-amphetamine, half-life = 11 hrs. O - - - O Excretion following ingestion of 12.5 mg. (corrected to 10 mg.) of a mixed *d*- and *dl*-amphetamine resinate (Product B), half-life = 26 hrs.

the resinate were placed in bottles which were revolved end over end at 12 r.p.m. in a constant temperature bath at 37° C. Simulated gastric juice was used for the first half hour followed by simulated intestinal juice, both prepared as recommended in the U.S.P. XV.[20] The contents of two capsules were placed in 100 ml. solution in bottles measuring approximately 8 cm. high and 4 cm. wide. It was found that the chief difference between the two products lay in the amount of drug released in the first 15 minutes—69% of Product A and 51% of Product B. After that time, the rates of release were similar so that in one hour 99% of the drug in Product A was released and 81% in Product B. The rates of release for 15-minute periods are shown in Fig. 7 to be relatively similar. In this case the recommended *in vitro* method apparently does not offer effective means of distinguishing between a product which demonstrated sustained release *in vivo* and one which did not.

Discussion

Nelson[11] has stated that a sustained release preparation should establish therapeutic blood levels and maintain them over a stated period of time. From the work of Swintosky *et al.*[10] this would mean that the rate of urinary excretion of the drug must also be relatively constant. It would therefore appear that urinary excretion rate offers a useful approach to the problem of evaluating sustained release preparations.

There is no doubt that variation between subjects and magnitude of blank excretion are important factors in the interpretation of urinary excretion tests, and that this is particularly true at the various time intervals during excretion of a drug. Nevertheless, since repeated tests of the same preparations yield essentially the same results it is not felt that this variation casts serious doubt on the conclusions reached with the three drugs reported here. Reproducibility of the recovery of drugs in different tests is within normal range encountered in good bioassays.

It is of interest to compare the results found with creatinine resinate in the present study with those obtained by Gillhespy *et al.*[3] As calculated from their Graph No. 3, from a dose of 900 mg. they obtained an excretion of 56% of the dose, which is much lower than that obtained in this laboratory (91-95%). Since their standard curve had returned to the blank excretion level at eight hours, this would appear to be the total excretable amount under their conditions. The literature[14] indicates that the excretion should be nearer 90%. No explanation can be offered for the fact that a similar if not identical resinate exhibited a delayed

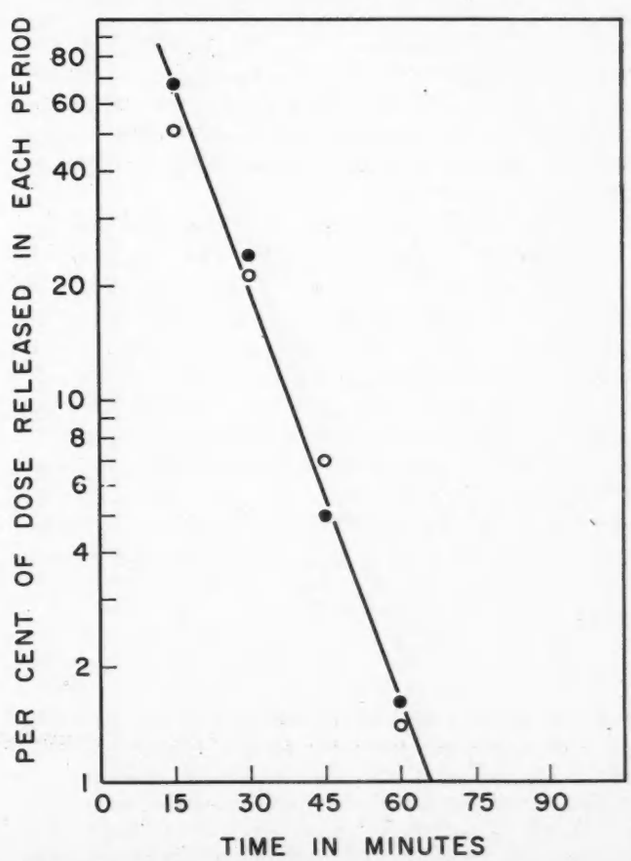

Fig. 7.—*In vitro* release of amphetamine from two drug-resin complexes. ● — Product A, O — Product B.

release in their hands but little evidence of either delayed or sustained release in this laboratory.

The fact that some preparations appear effective in producing sustained release when judged by clinical response and *in vitro* release,[1] and yet can be shown to be ineffective when judged by urinary excretion, raises an important point. It would appear that the criterion of clinical effectiveness may not be sufficiently critical to evaluate such effects. It is interesting to note that only in the work of Freed *et al.*,[4] where quantitative measurement of response was used, did the results correlate with those reported here.

It has been indicated[1, 4] that the side reactions with the amphetamine-resin complex are less and that the patients were more tolerant to it than to the ordinary form of the drug. It has not been shown that this greater tolerance could not have been simply a result of a lower dose of the drug caused by lower availability of the drug in the resinate form. The use of urinary excretion furnishes a measure of the physiological availability of the drug and therefore precision of dosage.

Abrahams and Linnell[1] stated that since the *in vitro* and *in vivo* results with creatinine resinate correspond and since sustained release has been demonstrated, it may reasonably be assumed that other drug resinates will also exhibit sustained release. In the present study, it was found that while the drugs from amphetamine resinate and acetylsalicylic acid resinate appear to be fully available *in vivo*, creatinine from creatinine resinate appeared to be somewhat less available. Hence, it may not be possible from the results obtained with one drug resinate to predict what results will be obtained using other drug resin complexes, although in this case one would have been correct in predicting a lack of sustained release from the creatinine data.

Blythe[12] and Campbell *et al.*[5, 6] pointed out that *in vitro* tests alone are of no value, but *in vitro* tests in which the release rates correlate with results of *in vivo* tests are indispensable as control procedures. The *in vitro* test used in the present study did not appear to differentiate clearly between a resinate with sustained action and one without such effect, although others[1] have reported that a similar test was useful for this purpose. Obviously, there is need for more critical comparison of *in vitro* and *in vivo* procedures before the former may be considered useful as control methods. There is also need for further development of *in vivo* procedures.

SUMMARY

In an attempt to develop an approach to the evaluation of sustained release, the rates of urinary excretion of creatinine, acetylsalicylic acid and amphetamine sulfate complexed with an ion exchange resin were compared, after single doses of the resinates, with the rates of excretion after dosages of the drugs themselves. It was demonstrated that while one resinate exhibited a sustained excretion rate, the other products showed little if any evidence of this property. The fact that products of the latter type, on the basis of clinical effectiveness and *in vitro* release tests, have been reported to show sustained release, demonstrates the need for more critical and quantitative evaluation of this type of medication. A sustained excretion effect was produced by repeated dosing with creatinine and acetylsalicylic acid. The value of urinary excretion data for studying sustained release was demonstrated. Using an *in vitro* test, it was not possible to differentiate clearly between the amphetamine resinate which exhibited sustained excretion rate *in vivo* and the resinate which did not. The need for more effective *in vitro* tests was emphasized.

The authors are grateful for the co-operation and assistance of the 12 subjects who volunteered for these studies.

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RÉSUMÉ

Le but de cet article est de comparer chez l'humain les taux d'excrétion urinaire de certains médicaments en forme pure et conjugués à une résine qui devrait en retarder l'absorption. Les auteurs ont aussi cherché à établir un rapport entre le taux de libération du produit conjugué *in vivo* (d'après l'excrétion) et son équivalent *in vitro*, selon une méthode qu'ils décrivent dans le texte. En l'occurence cette phase de leurs recherches s'est limitée uniquement à l'amphétamine. Les trois composés sur lesquels portèrent ces essais furent la créatinine, l'acide acétylsalicylique et le sulfate d'amphétamine. Douze volontaires en santé âgés de 29 à 44 ans prêtèrent leur concours. Les déterminations furent pratiquées sur une urine témoin et 14 échantillons prélevés jusqu'à 56 heures après l'administration des médicaments.

Jusqu'à 93% de la créatinine pure ingérée en solution furent recouvrés dans l'urine à comparer à 66-76% du complexe résineux. La période de ce produit sous ses deux formes est d'environ quatre heures. L'acide acétylsalicylique sous forme de résinat est récupérable 100% par l'organisme (alors que dans le cas de l'amphétamine, 9% de la dose administrée est retenue par la résine et n'arrive pas à se présenter sous une forme assimilable). Les courbes de libération de cet acide en forme pure ou conjuguée à la résine sont très semblables. Le résinat n'apporte donc

aucun prolongement utile ou sensible de la libération dans les voies gastro-intestinales. Une présentation commerciale de résinat de dextro-amphétamine mise à l'épreuve donna une période de neuf heures et aucune preuve d'action soutenue. Par contre un autre conjugué résineux de *d*- et de *dl*-amphétamine montra une libération prolongée d'importance thérapeutique appréciable. L'application aux formes de l'amphétamine de la méthode *in vitro* destinée à mesurer le taux de libération dans un appareil de laboratoire reproduisant les conditions du milieu gastrique et intestinal, n'a pas su recréer la différence observée entre eux *in vivo*.

On ne peut donc prédire la résistance au péristaltisme et à l'action des sucs digestifs du complexe que forme un nouveau médicament avec la résine et la portion qui en est présentée à l'organisme pour assimilation. Il découle de ces expériences que les épreuves *in vitro* ne sont pas prêtes à remplacer les épreuves *in vivo*.

Case Reports

MULTIPLE AND FAMILIAL INTRACRANIAL VASCULAR LESIONS*

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INTRACRANIAL arteriovenous angiomas are being found and treated with increasing frequency. Apparently it is not common for angiomas to be associated with other vascular lesions in the head. A review of five papers[1-5] reveals a total of 250 patients with proven angiomas of which only five had or possibly had multiple lesions. These are all in the report of Paterson and McKissock.[1] They consist of one patient with a confirmed angioma and "possibly a second angioma in the other hemisphere". Four other patients were thought to have aneurysms in addition to their angiomas. Two of these had multiple aneurysms.

It is becoming more common in cases of aneurysm to obtain a history of what might be interpreted as a subarachnoid hæmorrhage in one or more of the younger members of the family. It may become evident that the intracranial aneurysm is more of a familial vascular defect than is currently thought. This paper is a case report of a young woman with two cerebral angiomas and an aneurysm and of her mother who had an aneurysm.

CASE 1.—Mrs. M.S., a half-breed Indian woman aged 32, was admitted to the Winnipeg General Hospital on April 7, 1955, with a history of sudden loss of use of her right arm and leg and loss of speech six hours previously. She had not been unconscious. At examination the next day the patient, a well-nourished woman, could not speak, but could obey commands and was alert and co-operative. Her neck was not stiff. Optic fundi were normal. The lower right half of her face was weak and the right arm and leg were slightly spastic and totally immobile; an extensor plantar response was elicited. No sensory examination was attempted. Blood pressure was 130/60 mm. Hg. Radiographs of her skull and chest were read as normal. A complete blood count and sedimentation rate were normal. Wassermann reaction was negative.

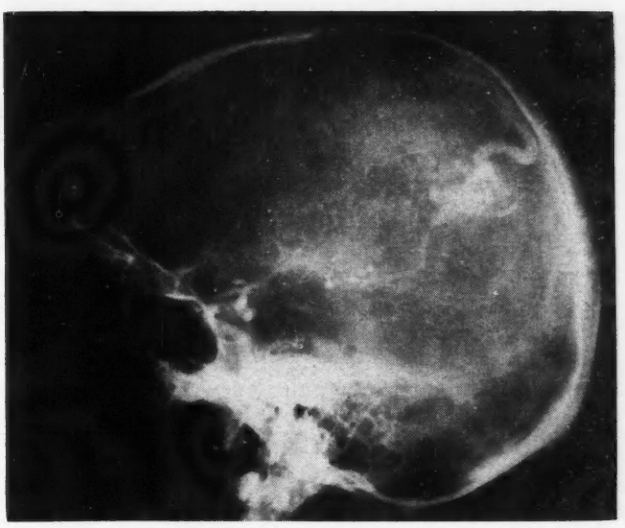

Fig. 1.—Mrs. M.S. Left carotid angiogram showing carotid siphon, middle cerebral artery, angioma, and a large emissary vein.

On April 11, left common carotid angiography was performed (Fig. 1) and reported by Dr. A. E. Childe as follows: "Satisfactory stereo lateral and A.P. projections have been obtained. There is filling of the carotid artery and the middle cerebral vessels. An arteriovenous malformation is outlined in the posterior part of the left parietal lobe. This is roughly 3 cm. in diameter and extends to within 1.5 cm. of the midline. At least two large emissary veins rapidly visualize and enter the sagittal sinus. No visualization of the anterior cerebral vessels has been obtained, presumably because of the vascular malformation."

On April 18, a craniotomy was performed by Dr. D. Parkinson and a left occipital bone flap was removed. The angioma was apparent on the surface, and the surrounding brain was stained yellow from an old hæmorrhage. The angioma was gradually mobilized by clipping and cutting the entering arteries and about 30 c.c. of solid and liquid clot was encountered at the lowermost aspect. When this was removed the remainder of the varix was mobilized with ease and the lower end could be seen to constitute the lateral wall of the lateral ventricle. A large vein was mobilized last and at this point it was noticed that the previously red contents were now blue, as in a normal vein. The vein was doubly ligated after milking the blood out between two fingers. The wound was closed with one drain in the angioma bed and one beneath the scalp.

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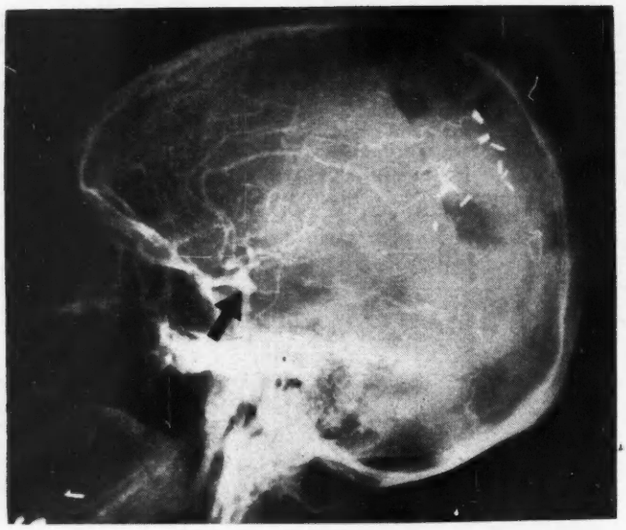

Fig. 2.—Mrs. M.S. Postoperative left carotid angiogram showing aneurysm which on stereoscopic examination proved to be on the middle cerebral artery at the trifurcation. The previous angioma is gone and the middle cerebral artery is now apparently smaller.

Her postoperative course was uneventful and by the time of her discharge from hospital on April 30, she had regained some speech. She was also able to walk and, although her right leg was spastic, her gait was reasonably good. After discharge from hospital she continued to improve although no function of the right arm appeared. Her speech in the six months after discharge continued to improve and became normal.

She was seen on December 19, 1956, and stated that the weakness of the right arm seemed to be increasing. She also thought that she was having more trouble walking. On re-examination her condition was thought to be exactly as it was at the time of her discharge 18 months previously. However, she was readmitted to hospital and a left carotid angiogram was again taken (Fig. 2). Dr. A. E. Childe reported that "good visualization has been obtained in both projections. There is no evidence of recurrence of the left-sided angioma previously seen. For the first time in any of the angiograms which have been performed on this patient, there is good visualization of the

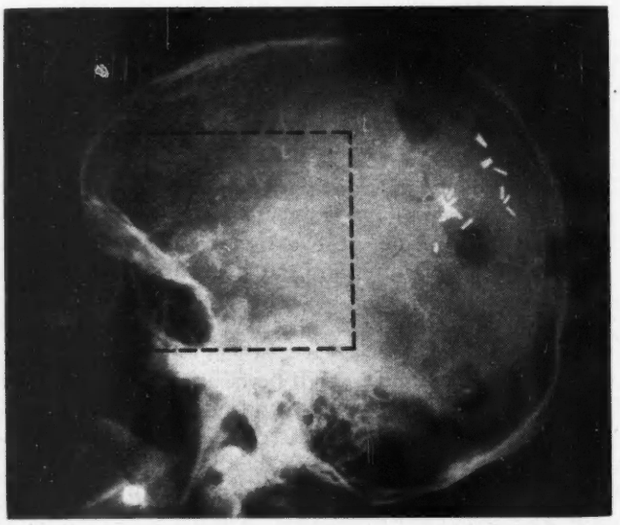

Fig. 3.—Mrs. M.S. Right common carotid angiogram, late arterial phase showing a small cluster angioma to the left of the centre of the boxed area.

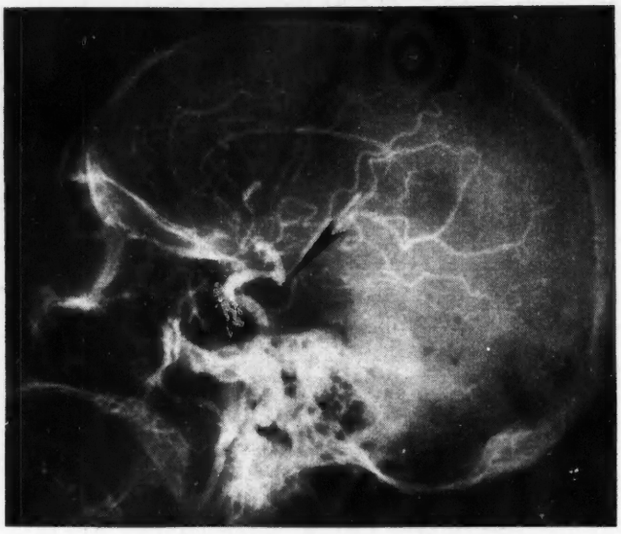

Fig. 4.—Mrs. B.D. Right carotid angiogram showing a small aneurysm at origin of posterior communicating artery.

anterior and middle cerebral arteries in the A.P. projection. It is now apparent that there is an aneurysm roughly 6 mm. in diameter originating from the left middle cerebral artery in the Sylvian fissure about 2.5 cm. to the left of the midline in the region where it trifurcates. This projects downward. A review of the previous angiogram also shows this aneurysm."

Because this patient had had an angioma and an aneurysm was now discovered, both in the left cerebral vessels, it was decided to take a right common carotid angiogram (Fig. 3). The report read: "Good visualization has been obtained in both projections. Reasonably late in the arterial phase a small cluster of vessels appears superficially on the right side in the anterior superior part of the middle fossa. No marked dilatation of any of these vessels is visible, and there are no large venous channels leading away from them. Nothing otherwise remarkable has been demonstrated on the right. These findings suggest a small, quite possibly unimportant superficial, right-sided angioma."

The patient has been seen at three-month intervals in the out-patient department and continues well. Though her right arm is almost useless, her walking is almost normal, and her speech is normal. No further surgery to her cranium is anticipated at the moment.

CASE 2.—Mrs. B.D., a 64-year-old half-breed Indian woman, was admitted to St. Boniface Hospital on June 29, 1957. Four hours previously she had suddenly become unconscious. Shortly after this she had had a generalized convulsion and had been rushed to the hospital.

She was unconscious but responded to painful stimuli by withdrawing the stimulated limb. She had no spontaneous movement. Respiration and pulse were rapid and her face was flushed. Pupils were in the mid position and reacted poorly. The neck was stiff. The right plantar response was extensor. Spinal puncture revealed a pressure of 350 mm. H_2O and produced a uniformly bloody fluid.

The next morning she responded to spoken speech and possibly her neck was somewhat less stiff. She gradually became more conscious in the next two or three days and when asked directly complained of a right-sided headache. By the time she regained full consciousness her blood pressure was found to be

155/80. Nine days after admission to hospital a right common carotid angiogram was taken under general anæsthesia (Fig. 4). It was interpreted as showing a small aneurysm which on stereoscopic views was found to stem from the origin of the posterior communicating artery directly on the carotid siphon. As this was thought to be a surgically unapproachable lesion, a Silverstone clamp was placed on the right carotid artery and gradually tightened. She was discharged from hospital on August 11 and died at home on August 20, of another subarachnoid hæmorrhage. This patient was the mother of the first patient presented above.

SUMMARY AND CONCLUSIONS

A case history is reported of a young woman found to have a left parieto-occipital angioma. On further investigation she was found also to have a large aneurysm arising from the left middle cerebral artery. A small additional angioma on the right side in the anterior superior part of the middle fossa was also discovered.

A short time after this patient's investigation and treatment, her mother was admitted to hospital and found to have an intracranial aneurysm. It is suggested that intracranial aneurysms and angiomas may be more common in several members of one family than is generally conceded.

I wish to thank Dr. L. G. Bell, Chief of Medicine, Winnipeg General Hospital, for permission to use the records of Mrs. M.S., and Dr. D. S. McEwen, Chief of Medicine, St. Boniface Hospital, for permission to use the records of Mrs. B.D.

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SEVERE HYPOPROTHROMBINÆMIA AFTER PROPYLTHIOURACIL THERAPY

GIOVANNI D'ANGELO* and
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THE TOXIC manifestations due to the use of propylthiouracil are well recognized. In most cases reported,[1-6] the toxic signs include fatal and non-fatal agranulocytosis, leukopenia, drug fever, fatal jaundice, swelling of submaxillary salivary gland and dermatitis; goitre in twins whose mother had received propylthiouracil during pregnancy has also been reported. Craddock[7] and Mirrer[8] each reported one case of severe hypoprothrombinæmia after propylthiouracil therapy in the absence of any liver injury.

A 60-year-old white diabetic woman was admitted to Maisonneuve Hospital on June 20, 1958, at 9:00 a.m. with severe epistaxis, ecchymosis, progressive fatigue for two weeks, and sore throat. The bleeding tendency was so severe that bleeding occurred at the site of venipunctures and could not be easily controlled.

The patient was well developed and well nourished but slightly pale. She was somewhat mentally confused but showed no icterus or axillary hypotrichosis.[18] Spleen and liver were not palpable. Blood pressure was 195/80 mm. Hg, temperature 101° F. and pulse 140/min. She had had 11 full-term pregnancies and the family history was negative. She had been in hospital during October 1954 for diabetes mellitus, hypertension and hyperthyroidism (which had been confirmed at the time by laboratory data). About two weeks before the present admission she had been started on 300 mg. of propylthiouracil daily. This medication had been added to digitoxin (Digitaline), reserpine (Serpasil), insulin, acetazolamide (Diamox), and ethinyl-œstradiol (Nadestryl) that she had been taking since 1954.

On admission the coagulogram showed: prothrombin time (Quick one-stage) 106 sec. (control 12 sec.); prothrombin consumption time 46.2 sec. (control 45 sec.); clotting time 38 min. (Lee and White modified); clot retraction satisfactory; Fibrindex* 5 sec. (control 5 sec.); platelet count 310,000 (Rees and Ecker); tourniquet test negative; bleeding time 12 min. 30 sec. (Ivy). Hb. 13.2 g. %; hæmatocrit 38%; sedimentation rate 51 mm. in one hour (Wintrobe); leukocyte count 17,600, neutrophils 75%. The smear revealed no morphological abnormalities of platelets or leukocytes.

Vitamin K_1 (Mephyton), 100 mg. in 500 c.c. of saline solution, was administered on the same day at 2:15 p.m. After eight hours the prothrombin time was 80 sec. and the bleeding was much more easily controlled. Vitamin K_1 administration was continued and dosage of 50-100 mg. was repeated six times during a period of three and a half days. The prothrombin time and other coagulation tests then reached normal limits. The patient was feeling much better and no signs of bleeding were noted.

Results of other laboratory tests on the day of admission were as follows: blood sugar 344 mg. %; blood urea nitrogen 139.5 mg. % (cause unknown); sugar in urine 42 mg./litre; urine specific gravity 1.025; urine pH 5.0, no acetone, no albumin. E.C.G.: sinus tachycardia; possibility of digitalis alterations.

Blood sugar and blood urea nitrogen determinations were repeated after the insulin therapy which was started on June 23 (20 units a day). On discharge, blood sugar was 122 mg. % and blood urea 38 mg. %. Laboratory tests on June 23 (three days after admission) gave the following results: hæmatocrit 32%; prothrombin time (Quick one-stage) 15.2 sec. (control 12.5 sec.); prothrombin consumption time 46 sec. (control 49 sec.); clotting time 16 min. (Lee and White, modified); bleeding time 1½ min. (Ivy); clot retraction satisfactory; platelet count 300,000 (Rees and Ecker); Fibrindex 5 sec.; tourniquet test negative.

*Chief, Department of Hæmatology, Maissoneuve Hospital, Montreal.

*Test based on the reaction of human thrombin with oxalated plasma. Normal value: less than 10 sec. Reagent supplied by Ortho Pharmaceutical Corp.

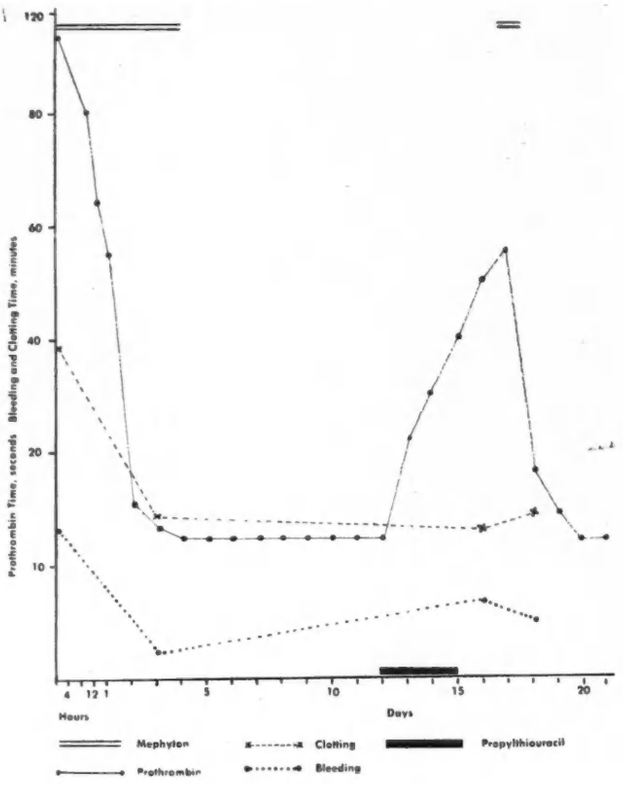

Fig. 1

Results of plasma electrophoresis, liver function tests and bacteriological and radiological examinations were all within normal limits. The Wassermann serological test was negative. The prothrombin time remained stable for a period of nine days without any therapy. The daily values are shown in Fig. 1. Because of the long illness of the patient and the numerous drugs she had received, it was difficult to determine which factor was responsible for the bleeding dyscrasia.

With the permission of the patient we readministered propylthiouracil. A dose of 250 mg. was given on July 3, and 50 mg. three times a day on July 4 and 5, amounting to a total of 550 mg. Before administration of propylthiouracil the prothrombin time was 12 sec. It rose gradually, and on July 7 the results of the coagulogram were as follows: prothrombin time 22.8 sec. (control 12 sec.); prothrombin consumption time 43 sec. (control 40 sec.); proconvertin 23.1 sec. (control 12.2 sec.); proaccelerin 14.6 sec. (control 13.8 sec.); clotting time 14 min. (Lee and White modified); clot retraction satisfactory; bleeding time 6 min. 30 sec. (Ivy); platelets 320,000 (Rees and Ecker); tourniquet test negative; Fibrindex 6 sec.

DISCUSSION

Propylthiouracil in our patient acted strictly as a coumarin-like anticoagulant affecting the prothrombin time, proconvertin (factor VII), clotting time of whole blood and, to a slight extent also, the bleeding time.

The readministration of propylthiouracil failed to reproduce a prolonged clotting time of whole blood after five days, but it must be remembered that dicoumarol has a slower effect on the clotting time of whole blood than on prothrombin.[9]

Some authors have reported that vitamin K failed to shorten prothrombin time or control hæmorrhage,[10] but others have claimed very satisfactory results.[12-14] Fresh normal serum has been reported effective in some cases,[7, 11] but the authors of these case reports have not established whether or not they were dealing with real hypoprothrombinæmia.

ACTH has also been tried but it was without effect on prothrombin and factor VII.[16] Mirrer[8] restored prothrombin time to normal and abolished hæmorrhage and hæmaturia by administration of vitamin K in whole blood. In our case, vitamin K_1 (Mephyton) was successful in correcting hypoprothrombinæmia and hypoproconvertinæmia.

The age of the patient and her negative family history eliminate the congenital type of hypoprothrombinæmia; the possibility of a hypoprothrombinæmia due to antibiotics[15, 17] is excluded since she had never taken any. (Certain antibiotics may alter the bacterial flora of the gut and deprive the liver of the building blocks of prothrombin). The possibility that the hypoprothrombinæmia was a side effect of the ingestion of reserpine is not excluded, for such an occurrence has been reported.[19]

The fact that readministration of propylthiouracil produced the same depressing effect on the prothrombin time suggests that this drug caused the hypoprothrombinæmia in our patient.

SUMMARY

A typical case of severe hypoprothrombinæmia after administration of propylthiouracil in the absence of liver damage, neutropenia or leukopenia is reported. A very satisfactory result was obtained by the injection of vitamin K_1 (Mephyton) in normal saline solution. After recovery, treatment was stopped and the prothrombin time remained 12 seconds or 100% without any bleeding manifestations. Nine days later, a test dose of propylthiouracil was readministered. A rapid fall in prothrombin and proconvertin (factor VII) times was observed without any change in the other coagulation factors. The prothrombin time was easily brought back to normal with vitamin K. The patient was examined periodically and last seen in April 1959. No sign of hæmorrhage whatsoever has been observed, the diabetes was controlled, and the blood pressure was 220/120.

We wish to thank Dr. Léopold A. Long, Hôtel-Dieu, Montreal, who performed the proconvertin and the proaccelerin tests for us, Dr. J. Bernier, Maisonneuve Hospital, and Dr. M. Lesage for granting us permission to study this case.

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RÉSUMÉ

Les auteurs rapportent un cas d'hypoprothrombinémie et hypoproconvertinémie avec hémorragie grave suivant l'administration de propylthiouracil, sans atteinte hépatique, neutropénie ou leucopénie.

Un résultat très satisfaisant a été obtenu avec la vitamine K_1 (Mephyton) en solution physiologique.

Après une omission prolongée la dyscrasie sanguine a été reproduite en réadministrant une petite dose de propylthiouracil.

CROSSED RENAL ECTOPIA WITHOUT FUSION*

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J. N. WARD-McQUAID, M.S., F.R.C.S.,‡
Nottingham, England

CROSSED renal ectopia without fusion is a very rare abnormality. Lee[1] surveyed the literature up to 1949, collecting 28 cases and adding one of his own. Diaz[2] in 1953 was the first to fix the ectopic kidney in its normal position. The most recent case was reported by Caine[3] when acute appendicitis was simulated in a boy of 15. This was considered to be the 18th case to be diagnosed during life: the kidney was not removed. Burford and Burford[4] reported two cases, in neither of which the kidney was removed. One was found at operation for appendicitis.

We are now presenting what is believed to be the 10th case of crossed renal ectopia without fusion to be diagnosed preoperatively. The patient complained of pain in the left side and was treated by nephrectomy.

W.P., a white man, aged 46, was first seen at the Mansfield General Hospital in May 1958, complaining of hæmaturia and upper left abdominal pain, radiating to the left groin, for the past month. The pain was severe and required morphine to control the initial attack. There were associated pyuria, pyrexia and frequency of micturition. There had been two episodes of gross hæmaturia. There was no relevant past history. Physical examination was not informative. The urine contained pus cells and cultured paracolon organisms. An intravenous pyelogram (Fig. 1) showed an apparently normal upper left urinary tract and neither renal outline nor function on the right side. Cystoscopy showed some trabeculation of the bladder. The right ureteric orifice was nearer to the midline than usual. A ureteric catheter passed easily, and retrograde examination showed the right kidney lying in the left iliac fossa and well below the normal left kidney (Fig. 2).

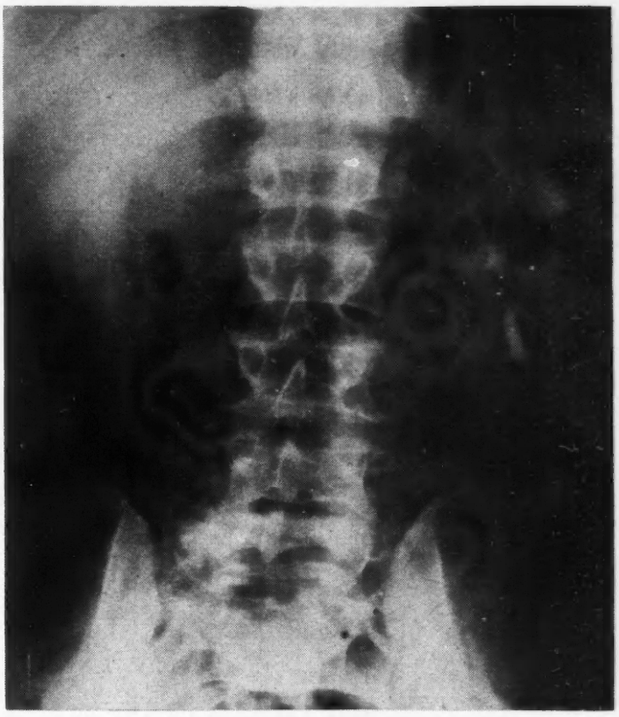

Fig. 1.—Intravenous pyelogram showing normal left kidney.

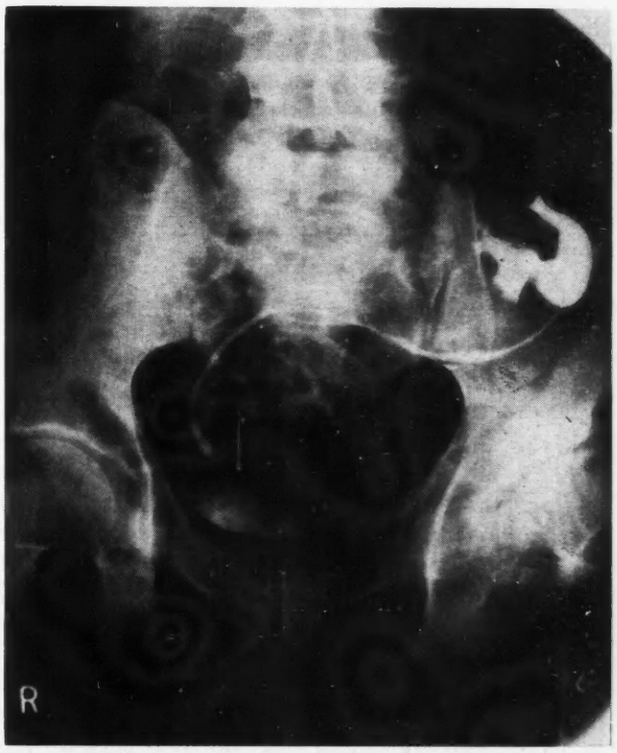

Fig. 2.—Right retrograde pyelogram showing kidney lying in left iliac fossa.

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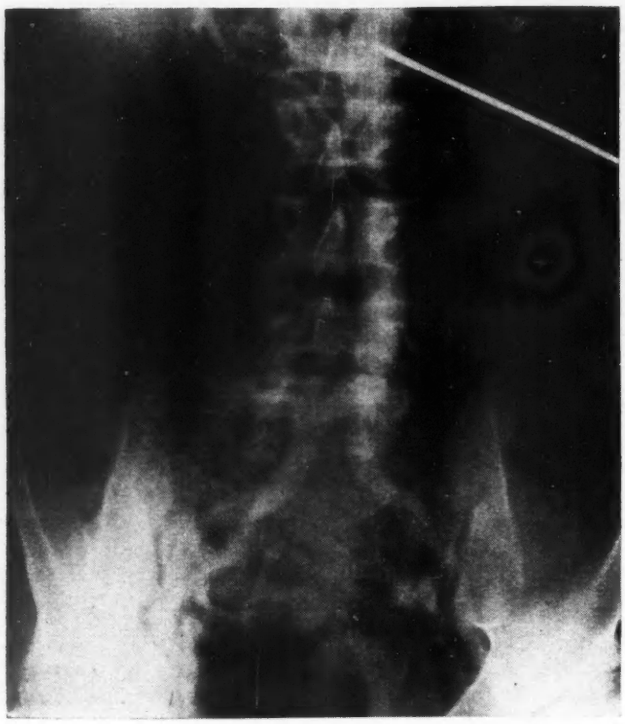

Fig. 3.—Aortogram showing vascular patterns of ectopic right kidney.

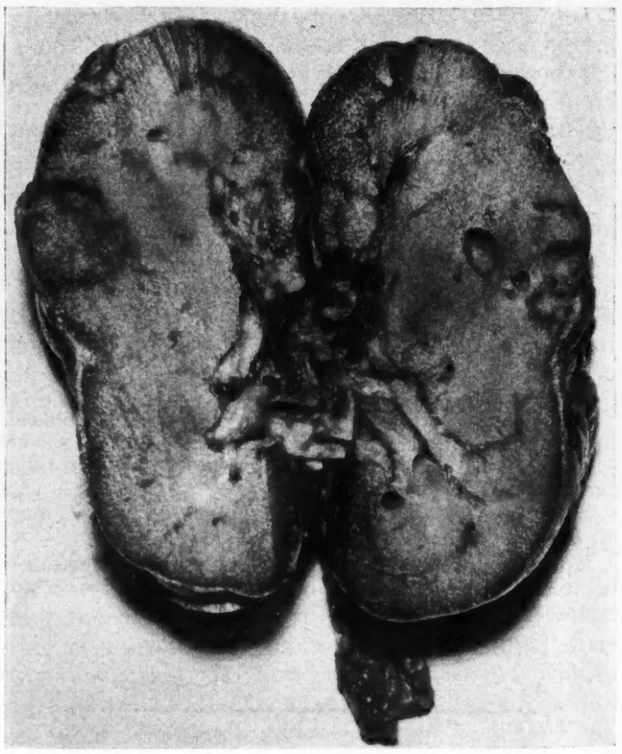

Fig. 4.—Specimen of excised kidney showing cortical abscess.

The pyuria continued. Paracolon organisms were cultured and found to be sensitive to nitrofurantoin (Furadantin). There was no clinical or bacteriological response to a full course of this drug. A further intravenous pyelogram showed no function of the ectopic kidney. Operation was therefore advised.

Translumbar aortography (Fig. 3) was carried out first under general anæsthesia by Dr. H. A. Buck. This outlined the vascular pattern of the ectopic right kidney, showing a leash of vessels from the aorta entering the kidney. The ectopic kidney could be felt with the patient anæsthetized. A left lower iliac muscle-cutting incision was then made, and the kidney exposed extraperitoneally. The perinephric fat was inflamed and there was an abscess in the cortex. Three arteries entered the upper pole and one the lower pole; all arose from the aorta (Fig. 4). There was a single renal vein, joining the vena cava. A nephro-ureterectomy was performed. Dr. A. MacFarlane confirmed the presence of a solitary abscess 1.5 cm. in diameter in the cortex, and on microscopy also reported multiple pyelonephritic scars. Convalescence was uneventful, and when last seen by us six months later, the patient was symptom-free and his urine was normal.

DISCUSSION

Males are involved at least twice as often as females in renal ectopia, and the left kidney is ectopic three times more often than the right. Bugbee and Losee[5] reported the only case in which both kidneys were crossed. The ectopic kidney is usually the lower of the two, although Ghoshal[6] had a case of crossed ectopic kidney which lay above the normal one. The pelvis of the ectopic kidney faces the spine. Its blood supply may arise from the aorta as in our case, from the iliac vessels, or from both the aorta and the iliac vessels. This is of importance when considering the surgical approach to the kidney and the possibility of replacing it in its rightful position.

Complications are likely in these kidneys, and in the 34 cases now reported, three had carcinoma of the kidney and 12 had infective or calculous disease. There are, of course, frequently no symptoms and signs unless those due to any complications ensue. Then there may be pain, a palpable mass, hypertension or pyuria. There is no doubt that many more cases are diagnosed than are reported, and again many cases are not diagnosed at all. Of the 34 reported cases, 13 were found at autopsy, five were diagnosed on pyelography alone and no operation was performed, and 10 were diagnosed before operation, but six more were not diagnosed until the abdomen was opened. Diaz has been the only one to treat the condition by replacing the kidney; in all the other patients with symptoms requiring radical surgery, a nephrectomy has been performed. The kidney in our case did not appear to be sufficiently healthy. However, the arrangement of the blood supply would have made replacement technically possible, had it been indicated.

SUMMARY

A patient with crossed renal ectopia complained of renal pain, frequency and hæmaturia. The diagnosis was made by pyelography and confirmed by aortography. Treatment was by nephrectomy because of persistent urinary infection, absence of function and a cortical abscess in the ectopic iliac kidney.

We are indebted to Dr. E. J. S. Townsend for the radiological reports and to Dr. A. MacFarlane for the histological work.

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SUBENDOCARDIAL FIBROELASTOSIS IN AN ADULT WOMAN

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IN 1816, Kreysig described a case of fibrosis of the endocardium under the term "fetal endocarditis".[1] Several types of endocardial fibrosis have since been described, among which is subendocardial fibroelastosis. The latter condition includes a proliferation of elastic as well as fibrous tissue. Several cases have been described in infancy and childhood but very few in adult life. This paper discusses the evolution of a case in an adult woman on whom a complete hæmodynamic study was performed. The diagnosis was made at autopsy.

Y.L., a 48-year-old white woman, enjoyed good health until August 1955, when she presented with an influenza-like syndrome including general malaise and a temperature of 103° F. The fever lasted only four or five days but over a period of eight to ten months the patient gradually developed a progressive dyspnœa, a dry cough, orthopnœa and dyspnœa even at rest. She lost 20 to 25 lb. of body weight. In May 1956, she was admitted to l'Enfant-Jésus Hospital, Quebec. On physical examination, she appeared orthopnœic and cyanosed. The jugular veins were distended. The heart appeared clinically enlarged and a gallop rhythm was heard. The right lung base was dull and silent. The liver was tender and palpable 4 cm. below the costal margin, in the mid-clavicular line. No œdema or ascites was noted. A chest radiograph confirmed the presence of a right hydrothorax. The heart was enlarged with a cardio-thoracic ratio of 18/27. A complete left bundle branch block and signs of dilatation of the left atrium were noted on the electrocardiogram. Hæmogram: red cell count 5,020,000; Hb. value 17 g. %; white cell count 6000, with the following differential count: neutrophils 47%, band forms 7%, eosinophils 11%, lymphocytes 30% and monocytes 5%.

Ordinary therapeutic means were used to control her congestive heart failure. Two consecutive thoracenteses produced respectively 800 and 650 c.c. of clear, straw-coloured, Rivalta-negative fluid. Cytological study showed multiple atypical cells, but none typical of malignancy. Cultures for pathogens and *Mycobacterium tuberculosis* were negative.

On the third hospital day, signs of thrombophlebitis of the right leg were first noticed. Local heat was applied, the limb was immobilized and anticoagulants were given. She was improved when discharged from hospital one month later, but the improvement was of short duration. Her symptoms of cough, exertional dyspnœa, orthopnœa and cyanosis returned and, in addition, she developed leg œdema. She had to be readmitted on September 15, 1956.

On examination, she appeared dyspnœic at rest and cyanosed. The jugular veins were distended. The heart was enlarged and a gallop rhythm was present. Rales were heard over both lung fields, the liver edge was 2 cm. below the costal margin and the legs were œdematous. There were no signs of ascites or pleural effusion. The same therapeutic measures improved her condition again. She was discharged on October 8, only to be readmitted two weeks later with the same clinical picture.

On November 18, 1956, she was transferred to the Montreal Institute of Cardiology for further investigation. On admission, the B.P. was 120/80 mm. Hg, the pulse rate 84, and the temperature 98° F. She appeared slightly cyanosed at rest and dyspnœic when answering questions. Her neck veins were distended. A nodule was felt in the right lobe of her thyroid. The thorax was symmetrical and the lungs were clear. The heart was enlarged clinically. On auscultation, the second pulmonary sound was accentuated and reduplicated, the second mitral sound was also reduplicated, and no murmur or gallop was present. The liver was palpable at the costal margin. There were no signs of ascites, pleural effusion or peripheral œdema.

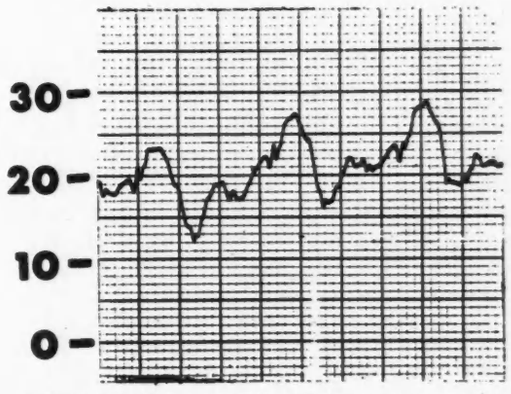

Fig. 1.—The pulmonary "capillary" pressure curve shows an M-shaped atrial pattern.

The chest radiograph revealed an increased translucency of the left upper lung field. The right pulmonary artery was slightly dilated and the left ventricle enlarged. The cardio-thoracic ratio was 17.5/25.5. The electrocardiogram showed a left bundle branch block with probable signs of left ventricular hypertrophy. Hæmoglobin level was 15.2 g. % and hæmatocrit 49.5%. The erythrocyte sedimentation rate was 28 mm. after one hour. The white blood cell count was 8252 with a differential count of 62% neutrophils, 4% eosinophils, 29% lymphocytes and 5% monocytes. The urine was normal. Blood urea was 34 mg. %, blood sugar 100 mg. % and cholesterol 233 mg. %.

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At cardiac catheterization (Fig. 1), the pulmonary "capillary" pressure curve showed an atrial "M". There was no "plateau of pressure" (Fig. 2) from the peripheral veins to the pulmonary "capillaries"; i.e., the mean pressure in the peripheral veins and the right atrium, the end-diastolic pressure in the right ventricle, the diastolic pressure in the pulmonary artery and the mean pulmonary "capillary" pressure differed by more than 5 mm. Hg.[2]

The angiocardiogram revealed an enlarged left ventricular chamber, the size of which did not vary much between systole and diastole. The vascularity was decreased in the left upper lung field (Fig. 3).

The final diagnoses were: (1) partial thrombosis of the left pulmonary artery; (2) myocarditis of unknown etiology, possibly of the Fiedler type. She was discharged from hospital on digitalis (Nativelle) 0.1 mg. daily and acetazolamide (Diamox) 375 mg. a day,

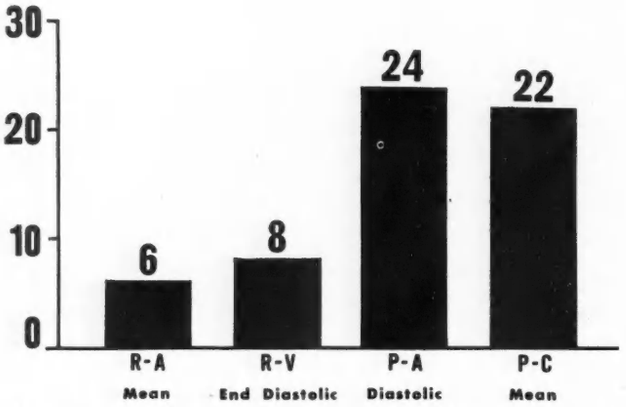

Fig. 2.—The mean pressure in the peripheral veins and right atrium, the end-diastolic pressure in the right ventricle, the diastolic pressure in the pulmonary artery and the mean pulmonary "capillary" pressure differ by more than 5 mm. Hg.

on the first four days of each week. Three weeks later, she developed a severe bronchitis. Her condition deteriorated rapidly and she died February 13, 1957, at l'Enfant-Jésus Hospital where she had been readmitted a week earlier.

An autopsy was performed by one of us (F.G.). On external examination, the patient appeared underweight but well developed. The jugular veins were distended. There was a soft œdema involving both lower extremities and the pre-sacral region. Autopsy was restricted to the thoracic viscera at the request of the family. The heart weighed 470 g. It appeared markedly hypertrophied (diameters: 17 × 11 × 10 cm.) and the four chambers were dilated, especially the right atrium and the two

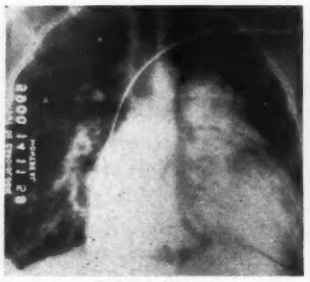

Fig. 3a

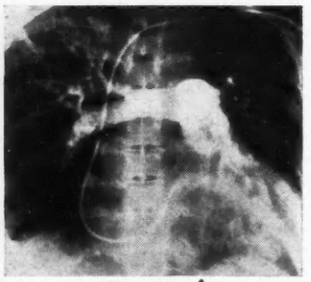

Fig. 3b

Fig. 3a.—Levogram: The left ventricular cavity is dilated.
Fig. 3b.—Dextrogram: Vascularity is decreased in the left upper lung field, suggesting partial obstruction of the right upper lobe artery.

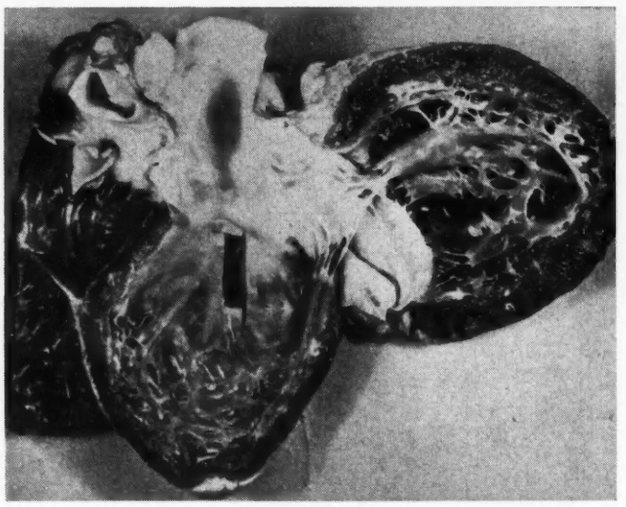

Fig. 4.—The left ventricular endocardium is white and smooth as compared to the right.

ventricles. The valve rings were dilated but otherwise of normal structure. Their circumference was: tricuspid, 12.5 cm.; pulmonary, 7.5 cm.; aortic, 7.0 cm.; and mitral 10.0 cm. The wall of the left ventricle was 10-14 cm. in thickness and the right 3-4 cm. The left ventricular endocardium, especially the septal wall, was white and smooth (Fig. 4). A small red thrombus, 10 mm. in diameter, was attached to the papillary muscles of the right ventricle. The venæ cavæ and coronary sinus were distended. The coronary arteries were soft and appeared normal. A few yellow atheromatous plaques were present on the intima of the aorta.

The right pleural cavity contained 2000 c.c. of reddish-brown fluid distributed in numerous collections separated by brownish membranes which also covered the pleural surfaces. The right lung weighed 600 g. The superior lobe was well aerated. The middle lobe was indurated and the cut surface red. The inferior lobe was collapsed, red and firm with a firmer bluish area at the periphery. The arterial branches to the middle and lower lobes were obliterated by a fresh, slightly adherent clot. Several small peripheral branches were thrombosed. The left pleura was adherent posteriorly. The left lung weighed 390 g. and appeared well aerated. The superior lobe presented a bluish firm area measuring 9 × 6 × 5 cm. in diameter. The arterial branch to this segment was obliterated by a fresh red thrombus.

Microscopically, the endocardium of the left ventricle was thickened, fibrous and rich in elastic fibres (Fig. 5a). One area of the specimen showed an agglomeration of hæmosiderin pigments (Fig. 5b). The cardiac muscle was otherwise normal. The pulmonary lesions proved to be areas of infarction of different ages, most of which were recent.

DISCUSSION

The etiology of this rare condition has been the object of many hypotheses. Monckeberg *et al.*[1] attributed subendocardial fibroelastosis to an inflammatory process occurring during fetal life and affecting either the mother or the fetus itself. Since it has never been possible to obtain evidence of such an inflammatory process in its acute stage in an embryo and since elastic hyperplasia is never

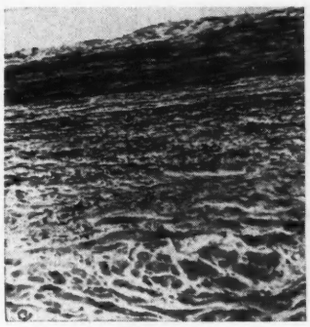

Fig. 5a

Fig. 5b

Fig. 5a.—The endocardium of the left ventricle is thickened, fibrous and rich in elastic fibres.

Fig. 5b.—Area showing an agglomeration of hæmosiderin pigment.

encountered elsewhere in an inflammatory reaction, this hypothesis is unlikely.

Subendocardial fibroelastosis has been placed in the family of collagen diseases.[3] Absence of the fibrinoid degeneration so characteristic of other collagen diseases makes this hypothesis doubtful.

The presence of hæmosiderin pigments has led to the belief that the process starts with the occlusion of a thebesian or arterio-luminal vessel. Consequently, there would be extravasation of blood, deposition of pigments and eventual fibrosis. Yet the presence of hæmosiderin pigment in subendocardial fibroelastosis can be explained by a pre-existing fibrosis progressing to the point of occluding vessels with resulting deposition of hæmosiderin pigment.[1, 4-7]

A transient anoxia in the course of development of the endocardium has been considered as an important factor in the pathogenesis of subendocardial fibroelastosis.[8-11]

According to Prior and Wyatt,[8] fibroelastosis is the result of a genetic disorder of the mesenchymes of unknown nature. The frequency of this condition among siblings would favour this opinion.

Even if some patients live to adult life, this does not discard the possibility of a congenital malformation. It seems logical to assume that the more severe the fibroelastotic process is, the earlier the patient is likely to die. The rapid deterioration of an adult patient with this lesion is similar to that of certain patients with congenital aortic stenosis who may enjoy a normal life for years before they succumb. In the latter condition, the patient is relatively well until the left ventricle can no longer accommodate for the increased work it must perform. It is likely that in subendocardial fibroelastosis the thickening of the endocardium hinders the contraction of the left ventricle and necessitates an effort greater than normal.[12] Once the left ventricle fails, the deterioration is very rapid. As for acquired or congenital aortic stenosis, the initial episode of failure may be precipitated by a respiratory infection. This was the case in our patient and we would like to consider this infectious process as a non-specific stress imposed on the left ventricle rather than a specific factor leading to fibrosis.

The only way to confirm a diagnosis of subendocardial fibroelastosis is to study a histological section of the tissue. Nevertheless, a clinical diagnosis must be entertained in the presence of left ventricular failure of unknown etiology. The chest radiograph shows an enlarged heart, the left ventricle being mainly involved. The electrocardiogram shows a systolic overload pattern of the left ventricle or a bundle branch block. The left ventricular hypertrophy is secondary to the load imposed on the left ventricle by the thickened endocardium. The left bundle branch block may be explained by the involvement of the left bundle branch in the fibroelastic process.

On cardiac catheterization, the patient with fibroelastosis of the left ventricle alone may present an M-shaped pulmonary capillary pulse tracing. This is far from being specific, since it may also be encountered in myocardial fibrosis of the left ventricle and in constrictive pericarditis involving mainly the left ventricle.[13]

The conditions to be considered in the differential diagnosis are multiple. Several cases of subendocardial fibroelastosis have come to operation with a false diagnosis of constrictive pericarditis.[13, 14] East African endomyofibrosis[15-17] has not been diagnosed as such on the North American continent, but other forms of endocardial fibrosis have been described. One type was described by Löffler in which endocardial fibrosis is accompanied by eosinophilia. The diagnosis is suggested by the blood picture.[18, 19] Still rarer conditions may simulate subendocardial fibroelastosis; these are beri-beri,[17] cardiac amyloidosis and glycogen storage disease of the heart, the latter being incompatible with adult life.

The prognosis in endocardial fibroelastosis is bad. The disease is usually fatal within a year after the appearance of the first signs of cardiac decompensation. No treatment has as yet been proven to be effective. Cures have been reported with high doses of digitalis or steroids, but since the diagnosis can be definitely proven only by histological study of the tissue, such therapeutic successes may be questioned.

SUMMARY

Different theories of pathogenesis of subendocardial fibroelastosis are reviewed. The case of a 48-year-old woman is presented with the clinical, hæmodynamic and pathological studies.

The survival of the patient until adult life is not incompatible with a congenital etiology. In milder cases of subendocardial fibroelastosis, a patient can remain asymptomatic for years, but once the first manifestations of congestive heart failure occur, the patient's condition deteriorates rapidly.

Although there are no pathognomonic signs for this condition, the diagnosis of subendocardial fibroelastosis of the left ventricle should be considered as a possibility in any case of left ventricular failure of unknown etiology.

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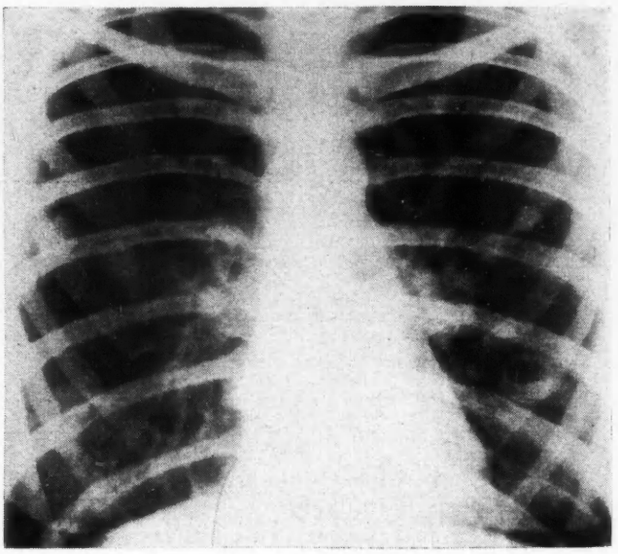

Fig. 1.—Chest roentgenogram taken May 25, 1951.

PULMONARY HISTOPLASMOSIS

W. J. WALKER, M.D. and E. C. JANES, M.B.,
Hamilton, Ont.

WITHIN THE LAST DECADE there have been several reports of histoplasmosis in Canada. These have included fatal cases in Ontario in the St. Thomas and Chatham area as reported by Haggar, Brown and Toplack,[1] as well as numerous benign cases.[2] In spite of the fact that histoplasmosis is apparently endemic in Southwestern Ontario, only three cases of active pulmonary histoplasmosis have been documented in Hamilton. One of these was a patient at the Mountain Sanatorium studied by Armstrong.[3] He was a 61-year-old man from Hamilton who died of coronary thrombosis in 1953. At autopsy, *Histoplasma capsulatum* was identified in consolidated areas and cavities in both lungs as well as in the hilar lymph nodes and bone marrow.

The second patient was a 57-year-old man who lived about 40 miles north of Hamilton. He had been under observation for many years because of suspected healed pulmonary tuberculosis. In November 1957, a nodular lesion appeared in the left lower lobe and was thought to be a carcinoma. It was removed at the Hamilton General Hospital on February 5, 1958, and proved to be a granulomatous lesion of histoplasmosis.

The third patient has been studied by us over a period of 11 years, and the case is reported below.

W.J.H. was first seen at the McGregor Clinic in 1948 at the age of 15 years. She gave a three-year history of recurring joint aches associated with fatigue. At no time had she had any pulmonary complaints. She had lived in Bolivia for the first three years of her life, during which time she had been well except for an attack of dysentery. From the age of three to 14 years she had lived in Southwestern Ontario, in London and Ridgetown. She then moved to Hamilton.

The results of physical examination, laboratory investigation and fluoroscopy of heart and lungs were normal on her first visit. During the following year her health improved but she fatigued easily.

In January 1951, while she was attending university, a routine chest radiograph was found to be abnormal. Throughout both lung fields there were scattered spherical lesions, most of which appeared to be solid and homogeneous although a few appeared cystic. A bronchoscopic examination was negative. A histoplasmin skin test (1:1000) was positive. Skin tests with coccidioidin, blastomycin, tuberculin, and hydatid cyst fluid were negative. The lesions slowly increased in size, as illustrated in Figs. 1 to 4. By 1953, the largest lesion was a cyst in the left lower lobe about 8 cm. in diameter. In spite of repeated negative Casoni skin tests, hydatid cyst disease was thought to be the most likely diagnosis.

On June 22, 1953, a left thoracotomy was performed at St. Joseph's Hospital by one of us (E.C.J.). About 12 localized caseous lesions were shelled out. No definite capsule was visible and the surrounding lung tissue appeared normal. The large cyst in the left lower lobe communicated with a bronchus. Microscopically, the lesions consisted essentially of caseous necrotic areas surrounded by a relatively thin rim of chronic granulomatous inflammation in which there was a

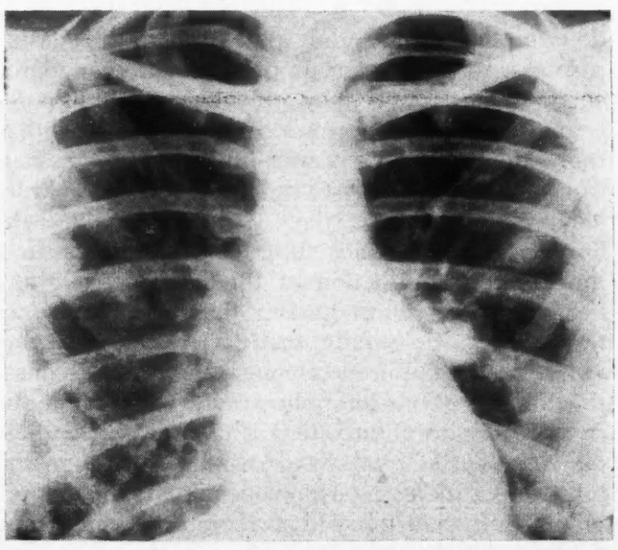

Fig. 2.—Chest roentgenogram taken May 21, 1952.

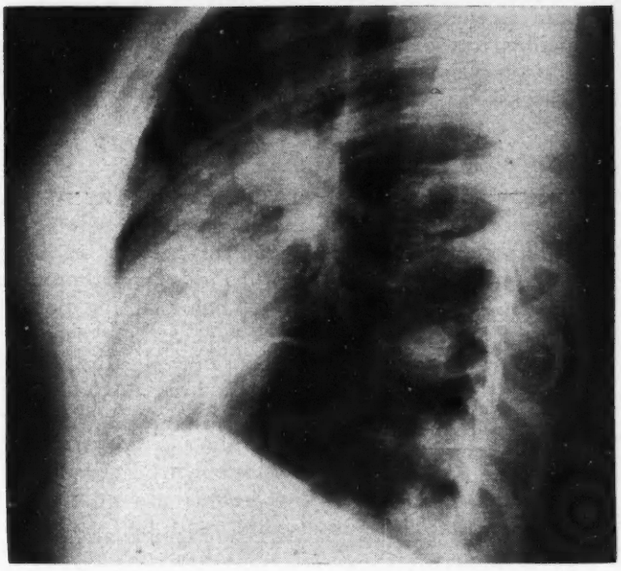

Fig. 3.—Chest roentgenogram (lateral view) taken March 23, 1953.

mixture of neutrophils, lymphocytes, epithelioid cells and occasional multinucleated giant cells. Fibrosis was minimal. Within the centre of these lesions there were small hyalinized rings which were thought to be artefacts. No bacteria or parasites could be identified, and smears and cultures for all types of organisms were uniformly negative. A diagnosis of granulomatous pulmonary lesions of unknown etiology was made.

About three months later, on September 10, 1953, a right thoracotomy was performed and eight similar lesions were removed from the right lung. The lesions were histologically similar to those previously removed. Representative sections were sent to various mycologists but no definite diagnosis could be made.

Since her operation, the patient has enjoyed good health. Laboratory studies have been normal except for a persistent elevation of the erythrocyte sedimentation rate which has remained around 40 mm. in one hour (Wintrobe). The white cell count has been about 12,000 with a normal differential. The urine has repeatedly shown a trace of albumin and one-plus red blood cells. Intravenous pyelograms in December 1955 and May 1958 were normal. Skin tests were

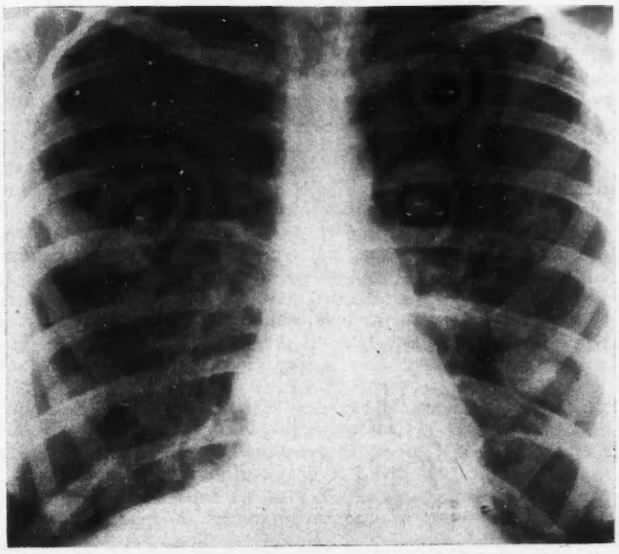

Fig. 4.—Chest roentgenogram taken May 21, 1953.

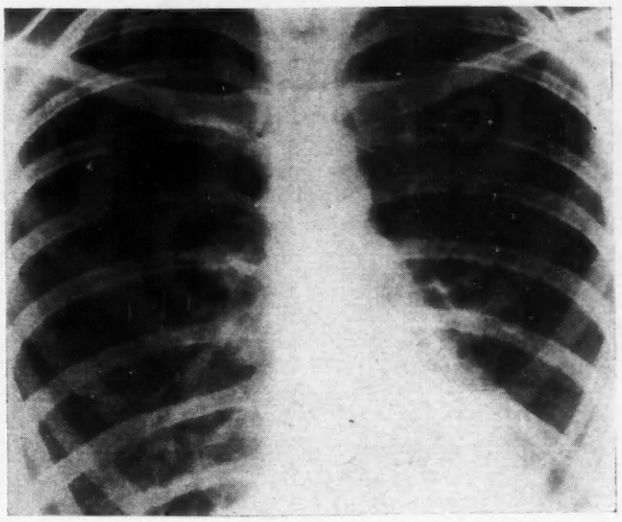

Fig. 5.—Chest roentgenogram taken April 29, 1954.

repeated and remained unchanged. A few lesions have reappeared (Figs. 5 and 6), but since 1956 there has been very little increase in their size.

In May 1958, the original pathological material was further investigated at St. Joseph's Hospital in Hamilton. By means of the Gridley fungus stain, small ring-like structures about three microns in diameter were identified which were morphologically identical with *Histoplasma capsulatum*. Since then, complement fixation tests for histoplasmosis have been carried out on five occasions. All have been positive in dilutions ranging from 1:16 to 1:64. Blood cultures for *Histoplasma capsulatum* were negative. No sputum has been available for study.

DISCUSSION

The diagnosis of chronic progressive pulmonary histoplasmosis was made on this patient on the basis of a positive histoplasmin skin test, positive complement fixation tests for histoplasmosis, and the presence of structures consistent with *Histoplasma capsulatum* in the lesions removed at operation. The diagnosis was not made for almost seven years after the first abnormal chest film. There were several reasons for this delay, the most important being failure to suspect the disease. Had the positive histoplasmin skin test found in 1951 been taken more seriously and followed through with complement fixation tests, the diagnosis of histoplasmosis would have been suspected earlier. However, the presence of cystic changes in some of the pulmonary lesions, and the fact that the patient once lived in Bolivia, made hydatid cyst disease seem most likely. Cystic changes in histoplasmosis must be extremely rare, although cavitation resembling that in tuberculosis is not unusual. Commonly, the lesions of histoplasmosis calcify, although it may take several years.[4] In our patient there had been no tendency to calcification. During the first two years of observation there was a marked increase in the size of the lesions. Even though the patient remained well, it was felt that dissemination of the disease was likely to occur unless some effort was made to halt the process.

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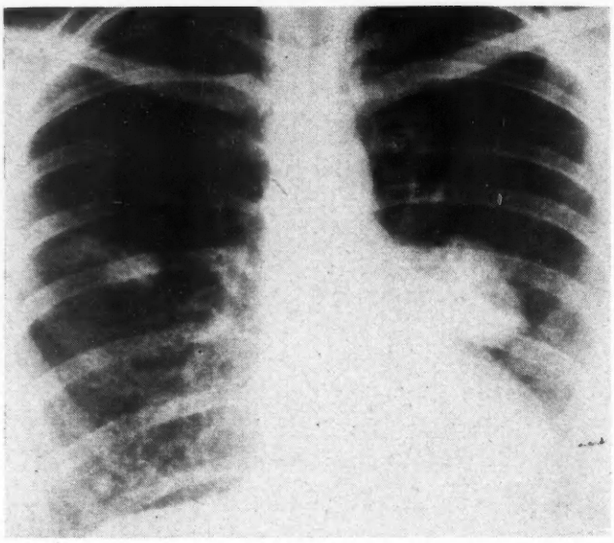

Fig. 6.—Chest roentgenogram taken February 21, 1959.

The decision to remove the lesions by surgery was made only after careful deliberation and consultation with others.

It is now appreciated that in benign, healed or slowly progressive disease, the organisms are very scarce or dead. Frequently, only the ghosts of the histoplasma remain, making identification difficult. Studies by Sweany[5] have also shown the difficulty in culturing the fungus in such lesions. In our patient, pathological diagnosis was made only after numerous sections had been taken and examined by various fungus stains.

The fact that the patient lived for 11 years in Southwestern Ontario, where the disease is probably endemic, may be significant. It is likely that she inhaled dust[6] containing the spores of *Histoplasma capsulatum* when she lived in this region. Failure to obtain a history of pulmonary symptoms, as in our patient, is not unusual, although the multiple lesions would suggest heavy exposure to the fungus.

Operation has been performed safely in pulmonary histoplasmosis,[7] but, as far as we know, not in such widespread disease as in this patient. Since her operations in 1953, lesions have reappeared in both lungs. These probably represent enlargement of nodules which were too small to be seen at the time of operation. The lesions near the left hilum could be a recurrence.

Although amphotericin B is now available and has been found useful[8, 9] in the treatment of histoplasmosis, we are inclined merely to observe the patient at the present time. She is well clinically, and during the past three years there has been very little tendency for the lesions to increase in size. We hope that the progress of the disease will become arrested and that the lesions will calcify.

SUMMARY

An unusual case of chronic progressive pulmonary histoplasmosis in a 26-year-old woman who once lived in Southwestern Ontario has been presented. The patient is well six years after the surgical removal of numerous histoplasmomas and cysts from both lungs.

The problems encountered in making the diagnosis are discussed.

ADDENDUM

After the preparation of this paper, Dr. M. L. Furcolow[10] reviewed the manuscript. He points out that, although the diagnosis on this patient is likely histoplasmosis, the progression of the lesions, the cystic cavitation and the apparent well-being of the patient are not entirely typical of this disease. He suggests that in the future some related fungus may be discovered which will give this picture. Dr. Furcolow and his colleagues also believe that the patient should be treated now for several reasons. She has not managed her disease well, results of complement fixation tests have remained elevated, the lesions are no smaller and, finally, she is getting older and her resistance may decrease.

We are indebted to Dr. Robert Haggar, Chief of Pathology at St. Joseph's Hospital, Hamilton, for his invaluable help in this case.

We also wish to acknowledge the assistance of Dr. Michael L. Furcolow, Medical Director of the Kansas City Field Station, Kansas City, Kansas, who reviewed the case, and offered helpful comments.

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THE USE AND ABUSE OF BLOOD TRANSFUSION IN OBSTETRICS

"The dramatic and gratifying decline in maternal mortality which has occurred during the lifetime of our older colleagues is due primarily to three innovations: (1) the replacement of blood loss; (2) the control of infection by antimicrobial drugs; (3) the improvement in indications for and technique of Cæsarean section. Each of these developments carries with it intrinsic dangers. The simplicity and safety of abdominal delivery has led to its abuse by those who see the obstetrician rather than the mother and her baby as the central figure in the obstetrical situation. The abuse of antimicrobial drugs has led in some instances to a tolerant attitude toward careless technique and also to the development of resistant strains of bacteria and the unrestrained growth of certain fungi. The abuse of blood transfusion has given rise to evils among which are: a false sense of security in the face of danger; a disregard for iron deficiency states; inadequate diagnosis and faulty treatment of anæmias; complications from blood transfusion itself, including immediate reactions due to incompatibility, delayed complications such as hepatitis and renal damage, and "occult" sensitization leading to hæmolytic disease in later pregnancies or reaction to subsequent transfusion."—S. C. Robinson, *Nova Scotia M. Bull.*, 38: 201, 1959.

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Special Article

REASONING IN RESEARCH*

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IT IS A COMMON ERROR to underestimate the power of the printed word. The publication of any research project in a medical journal tends to lend to the work an air of respectability that may be undeserved. It is suggested that neither those who write in the journals nor those who read them are always careful enough in the assessment of the work done. This is not merely a matter of academic interest, for the publication of a bad paper or the misinterpretation of a good one may lead to unfortunate repercussions in practice.

Medical research in earlier times was perhaps easier than it is now. "Why think?", wrote John Hunter to Jenner, "Why not try the experiment?"[1] When it is recalled that he later developed tertiary syphilis from his courageous experiments, one wonders if this advice was suitable even in his day and age. Nonetheless, so much lay undiscovered in those days that the spirit of clinical enquiry was more easily rewarded. The sort of research that most of us do now is more in the nature of evolution than of revolution. Recently there has been a gradual realization that we may even have to enlist the aid of statistical knowledge in order to consolidate our advances. This realization has not always achieved the results desired. There are times when the medical man presents his data to a statistician and comes up with some astonishing conclusions that would test the credulity of a congenital idiot.

The more intellectual atmosphere of the research laboratory seems to lend itself naturally to the development of sound experimental methods. On the other hand, those of us whose "laboratory" is the sick room may have lagged behind in realizing the difficulties involved and the disciplines necessary in the organization of a clinical research program. It is surprising then to hear a good deal of malicious comment about the place of statistics in our work. Some doctors adhere vociferously to the view that "statistics can prove anything", whilst others are easily convinced by a mass of imposing statistical tables. Who are the less discerning? The obvious need is for more knowledgeable criticism on the one hand and less gullibility on the other.

THE ORGANIZATION OF CLINICAL RESEARCH

Agnes Arber[2] outlines six logical steps to follow when investigating in the biological field; she has called this "the biologist's road to reality": (1) Choosing the question; (2) collection of the data; (3) interpretation of the results; (4) testing the validity in any conclusion; (5) writing up the work done; (6) final contemplation of the work.

*Abridged version of a paper read before the Staff and Guests of the McGregor Clinic, December 9, 1958.
From the McGregor Clinic, 250 Main St. E., Hamilton, Ont.

1. *Choosing the question*

This step is not by any means as easy as may appear at first sight. For example, one can ask, "What is the cause of cancer?" Given this assignment and an enormous monetary grant, any researcher would be hard put to know where to start. Obviously the immediate aim must be more definitive. Ask your researcher to explain why there is a greater incidence of carcinoma of the cervix in those who marry young and he may get closer to the fundamental truth, or at least he has a definite starting point for his investigations. It takes a rare gift of insight to be able to pose suitable questions with which to start a chain of productive research.

Russell, in a most valuable paper,[3] illustrated the six steps in a pattern I propose to follow, using as a basis examples from some simple investigations that I conducted in his department,[4] adding here and there other material to broaden the discussion. On this occasion, the general intention was to find some method of improving the management of the third stage of labour as conducted by the unassisted midwife. The more specific question was whether or not the routine administration of an ergometrine-hyaluronidase mixture lowered the incidence of postpartum hæmorrhage. A series of 697 normal primigravidæ was part of this experiment.

2. *Collecting the data*

The second step was the collection of the data. It was found that in these primigravidæ, 419 controls had 26 postpartum hæmorrhages, whilst of 278 patients given ergometrine with hyaluronidase, seven had a postpartum hæmorrhage (Table I).

TABLE I.—THE NULL HYPOTHESIS—PRIMARY POSTPARTUM HÆMORRHAGE IN PRIMIGRAVIDÆ

	Postpartum hæmorrhage		*No postpartum hæmorrhage*		
	Observed	*Expected*	*Observed*	*Expected*	*Totals*
Controls	26	19.8	393	399.2	419
Treated...	7	13.2	271	264.8	278
Totals....	33		664		697

It is unfortunate but true that it is common to find errors arising at this early stage. It is essential that the figures collected should be correct, because if they are not there is no point in examining them further. It is especially reprehensible to apply techniques of statistical analysis to incorrect data.

Where can errors arise in the collection of such apparently simple data? There are three main possibilities: faulty observation, faulty recording and the existence of bias.

Faulty observation.—Before attempting to measure the amount of postpartum bleeding, the term postpartum hæmorrhage must be defined. In Great Britain and North America, varying arbitrary standards have been adopted for record purposes. However, such inflexible standards do not allow the inclusion of many abnormal third-

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stage hæmorrhages, which stop short of postpartum hæmorrhage by definition. A careful investigation must make allowance for this.[5] But the difficulties of setting a standard are not nearly as great as the difficulties of accurately measuring third-stage blood loss. Those who have witnessed a severe postpartum hæmorrhage may wonder why it is not measured by the boot-full! This was not the standard we adopted, but a great deal of trouble was taken to try to measure blood loss accurately. This is not easy to do, but the effort must be made. One is not always impressed that sufficient care has been taken in many studies of postpartum bleeding. It seems pertinent to mention here that the inherent weakness of many studies lies in the acceptance of observations that are mainly subjective or hearsay. This accounts for much of the confusion arising out of studies concerned with, say, functional uterine bleeding.

Faulty recording.—It is unlikely, in a planned research program, that faulty recording of data would be a problem. But not infrequently one reads reports which utilize material abstracted from hospital records or the standard death certificates. Would it be uncharitable to regard such material as being sometimes unreliable? Nevertheless, I recall several hospitals in England where the quality of the records made them very suitable for retrospective analysis.

Bias.—The sources of error that may creep in because of abnormal bias are legion. In our example, great care had to be exercised to seek and eliminate such errors. It has been well said that if you compare chalk with cheese, you must not be surprised if the answer is a lemon. In any comparative survey, it is essential that the patients studied should in fact be comparable. This is not always easy in the biological field, especially when dealing with a condition like atonic postpartum uterine bleeding where the etiology is often unknown. Again, the attempt must be made, but is it always? It is an interesting exercise to prepare a list of possible sources of error in comparing the incidence of postpartum hæmorrhage. To mention some important factors, general anæsthesia, long labours, obstetric trauma and instrumental delivery have to be carefully evaluated.

Here a word of caution is indicated for those who may believe that the study of a large series of cases will always obviate the risks of bias. Such a procedure will only do so provided there are only random errors rather than systematic errors. The occasional inclusion of a case wrongly recorded as a postpartum hæmorrhage is an example of a random error. But if for some reason most of the primiparas were in the control group, this would be a systematic error. This is the sort of thing that Russell must have had in mind when he wrote—"Though random errors may be presumed to cancel out as the numbers increase, systematic errors will not be eliminated by increasing the numbers." Furthermore, the study of a very large series of cases increases the chances of other sources of error. When an investigator (or panel of investigators) attempts to observe, say, 10,000 cases, you will appreciate the great difficulties he may have in maintaining an accurate standard of reporting. The astute reader of such reports will always bear this in mind. It is always pleasant to recall that Sir James Mackenzie did a lot of his valuable early researches upon a comparatively few cases from a general practice in Burnley. Those who later sought to entice him to London were surprised that merely ten hospital beds would suit his requirements.

3. *The interpretation of the results*

In our example, the interpretation of the results rests upon the testing of a hypothesis, in this case, that of "no relationship" or the "null hypothesis", which on this occasion may be stated thus: "the postpartum hæmorrhage rate is not influenced by the treatment employed". Those who would like a more complete understanding of the application of this hypothesis are referred to Russell's original paper. In summary, tests of statistical significance are no more than measures of the differences between observation and expectation. In our example, to obtain a measure of this difference, we start by calculating the expected number in the top left-hand cell of Table I by the sum $\frac{33 \times 419}{697} = 19.8$.

Subtraction then gives us the marginal totals in the other three cells. To reduce our difference between observation and expectation to one value including all the essential data, the sum of the observed number minus the expected number, squared, is divided by the expected number in all four cells, and then added together. This value is known as chi-square (χ^2).

You may think that we are not really very far forward by all this, for although we have devised a method of expressing the difference between observation and expectation in one number, that is, the value of χ^2, we can still only say that the nearer to zero χ^2 is found to be, the more likely is the null hypothesis to be true, and vice versa. It is here that the statisticians come to our aid by preparing a set of tables which tell us that 95 per cent of the values of chi-square (computed from this type of table) likely to happen by chance lie between zero and 3.84. Now we have something really interesting, for this provides us with the knowledge that if the value of chi-square exceeds 3.84, then either a 5% chance (1 in 20) has come off, or a real underlying difference exists.

This is what statisticians mean when they say that the differences observed are "significant at the 5 per cent level". Please note that this does not give a cast-iron assurance that a genuine underlying difference has been demonstrated, because although long shots rarely come off, there is the occasional exception. It may be wondered therefore why we should not increase the value of chi-square to a level which would reduce the risk to, say, 1 in 100 (this happens to be 6.64). However, it is only fair to point out that by adopting this standard a new risk is introduced, namely, there is a danger that a real underlying difference may be overlooked and merely attributed to chance. So it is that statisticians advise us to steer a middle course and use the 5 per cent level as our critical standard. The conventional method

of expressing a value of x^2 which has been calculated to be significant at that level is to say that the probability (p) is less than 0.05.

To return once again to our example, the value of chi-square was calculated to be 5.1. This tells us that the probability (p) is less than 0.05, and therefore we would be fairly safe in drawing the conclusion that the observed difference between the postpartum hæmorrhage rate in the controls and the treated cases was almost certainly a real difference. The obvious inference is that the treatment reduced the postpartum hæmorrhage rate. This may be so, but there are several pitfalls for the unwary at this, our fourth step.

4. *The testing of the validity in any conclusion*

Just because a difference is found to be statistically significant, this does not explain the difference. Although in our investigation, the injection of ergometrine might have been expected to produce better uterine contraction and retraction, and although the addition of hyaluronidase might be expected to accelerate the absorption of the drug and enhance its effect, the experiment does not absolutely prove either. For instance, a similar trial using ergometrine alone or hyaluronidase alone might reveal improved results with either drug or only with one of them. The injection of an inert placebo might, by psychosomatic means, also produce a good effect. The midwife preoccupied with giving an injection keeps her hands off the fundus at a critical time, and this could influence third-stage bleeding. It is in the consideration of such factors that the trained researcher may turn up something of real but unexpected value. For instance, suppose it was found that hyaluronidase alone decreased the number of postpartum hæmorrhages, an entirely unexpected result, but one raising new vistas in the study of uterine physiology. This is the sort of situation that led the great Louis Pasteur to observe in his inaugural address at Lille, "In the field of observation, chance only favours the mind that is prepared." Those clinicians who keep a spirit of enquiry alive may find some consolation in the possibility that the experience gained in fruitless researches may be preparing their minds for at least one worth-while achievement in a lifetime.

In our example, we are dealing with a comparative survey, so please look again at the results in the control group. A quick calculation will show that the postpartum hæmorrhage rate was 6.2 per cent. You may think that this is somewhat high, and you could be right. In other words, the differences observed in the postpartum hæmorrhage rates might be due not to the benefits of prophylactic treatment, but to some unrecognized factor producing an unusually high postpartum hæmorrhage rate in the controls. It is useful in reading comparative reports to turn first to the control results and see if they tally with your own experience. It is then easy to accept with reserve the results of, say, the group recommending a new progestational agent for the treatment of threatened abortion who observed a control group with an abortion rate of 84.5 per cent.[6]

5. *The writing up of the work done*

This is, in many ways, the most difficult part of the work. Possibly more errors are committed at this stage than in any of the foregoing. I will attempt to outline some of the more obvious pitfalls. The pattern followed and the material and verbal fallacies related here are not new; they were described by Aristotle.

The fallacy of accident.—Here, the author confuses what is accidental (using the word in the sense of being non-essential) with that which is essential in the structure of his arguments. It is possible that obstetricians have perpetuated this fallacy regarding the syndrome of pre-eclampsia. For many years, this syndrome of œdema, hypertension and albuminuria has been recognized. However, as Scott[7] has recently re-emphasized, the diagnosis has always been acceptable if any two of these signs be present. It is difficult to think of any other condition in medicine where the presence of two physical signs results in an automatic diagnosis. This leads us back to a more fundamental consideration that there may be not one pre-eclampsia, but many.

The fallacy of the general in relation to the particular.—This is an old friend. For example, the procedures of classical Cæsarean section, subtotal hysterectomy and chloroform anæsthesia have, for some time, been recognized as generally undesirable. But teaching roundly condemning these procedures has often led to disastrous results in the individual case. One may quote as examples the attempt at low cervical section in the presence of an anterior cervical fibroid, or total hysterectomy with dangerous proximity of the ureters in a really difficult case of endometriosis, or of the attempt by the occasional anæsthetist to use an unfamiliar machine in urgent circumstances where the "rag and bottle" would have done.

The reverse of this argument is perhaps more common. The outstanding result of a single case may continue to cloud a man's judgment for years. But how difficult it is to remain philosophically detached when a good friend dies from cancer in an ovary left behind a few years before. Incidentally, are not gynæcologists a bit illogical when they argue strongly for routine removal of the ovaries in the menopausal age group at abdominal hysterectomy, yet find the indications less pressing when they do the operation by the vaginal route?

The fallacy of personality.—Lawyers use this fallacy when, having no real case, they seek to discredit the witnesses or abuse the plaintiff's attorney. Because a doctor has made some major contribution to medical progress, this does not bestow upon him the gift of always being right. So beware of the writer who finds it necessary to prop up his arguments by frequent reference to respected authorities. As an example of the perpetuation of this fallacy in the recent gynæcological literature, one can cite the work of Malpas.[8] This eminent man calculated the prognosis in cases of recurrent abortion. The outlook after three consecutive abortions was, apparently, very gloomy. For several years, at the beginning of nearly every paper on the subject of habitual abortion, this work was quoted. It was some time before anyone

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noticed that a cure rate of around 70 per cent was obtainable with a variety of remedies from vitamin E to bathing in ice-cold water. Although there are many other facets to this difficult subject, it seems possible from the observations of Bevis[9] that the spontaneous recovery rate without therapy may be at least as good.

This fallacy can mislead in the opposite way. "Give a dog a bad name and it sticks" says the old proverb. There is, in the north of England, a gynæcologist who has never received sufficient credit for recognizing and treating since 1931 cases bearing an uncommon resemblance to the condition we now name after Stein and Leventhal. But this man is such an original thinker and such an intrepid investigator, that he is not always taken too seriously. He once admitted a woman with Rhesus antibodies with the intention of giving *her* an exchange transfusion! Medical history abounds with examples of men who propounded a good deal of nonsense with great persuasion or a good deal of truth without success. Galen must have been an engaging personality to convince with some of his material whilst poor Semmelweis must have had a very poor manner of presentation.

The fallacy of popularity.—Here, a weak argument is supported by appealing to popular sentiment. I included an example earlier in the text. Consider the observation, "those of us whose laboratory is the sick-room". Such a remark gently flatters those who fancy themselves as clinical investigators, gently chides those who do not. Either way, the ground is prepared for a less critical attitude to subsequent arguments.

The fallacy of exploiting fear.—The fear motive is often exploited in order to gain a point. A good obstetric example of this is the attitude displayed toward the amniotic membranes. At the turn of the century, obstetricians were dealing with an enormous amount of cephalo-pelvic disproportion at a time when aseptic and antiseptic methods were rudimentary. The valid fears they developed in cases of premature rupture of the membranes linger with us to the present day. So it is that despite accumulated evidence to the contrary,[10] it is still common to regard intact membranes as an advantageous feature of normal labour.

A closely related problem is what to do when surgical induction is indicated, but the head is not engaged. The fear here is that of prolapse of the umbilical cord. This fear is entirely justified, but is not always balanced by the consideration that, in the first place, cord prolapse is distinctly uncommon despite the many cases in which the situation would appear to favour it, and secondly, the risk is inherent in any patient where the membranes rupture with the head still free whether this is done deliberately or not. Where induction is indicated, I do not hesitate to rupture membranes even if the head is not engaged. Surely the risk of cord prolapse when the obstetrician ruptures the membranes in the operating room does not exceed that of spontaneous cord prolapse in the first-stage room with the obstetrician on his way home to dinner?

Arguing in a circle.—It is extraodinary how often the researcher into pre-eclampsia finds himself on this merry-go-round. The elements of this fallacy are present in even the very important arguments of F. J. Browne;[11] briefly, in normal pregnancy there is a tendency towards hypertension due to adrenocortical activity. This is normally offset by the production of anti-pressor substances from the placenta. This may be deficient in pre-eclampsia when there is placental ischæmia, which may be due to reduced placental blood flow. This in turn may be caused by reduced uterine blood flow which in some cases may be caused by essential hypertension.

The fallacy of the consequent.—There has recently been perhaps too much concern about the phenomenon of afibrinogenæmia or hypofibrinogenæmia in pregnancy. The numerous cardiac patients on regular anticoagulant therapy would probably view with mixed feelings the antics of the average obstetrician encountering a clotting defect. The essentials of this fallacy are as follows: afibrinogenæmia interferes with normal blood coagulation, which leads to hæmorrhage; fetal death *in utero* may lead to afibrinogenæmia; therefore fetal death with afibrinogenæmia will lead to maternal postpartum hæmorrhage. The obstetrician who exercises restraint knows that this is very rarely true. Even a Couvelaire uterus usually contracts and retracts well, and this is what really matters. Occasionally fibrinogen is required, but even then, the spectacle of the obstetrician blundering about the hospital in search of this elusive substance would be amusing if meantime his patient were not quietly slipping away for want of adequate blood volume.

The fallacy of false cause.—In this fallacy, the conclusions drawn may be wrong because the data collected are erroneous, there has been an error in sampling or insufficient observations have been made. Reference to the collection of false data was made earlier in this paper. It is only necessary to emphasize that statistics is a very exact science which can only be debased by its application to faulty data.

We have a very important example of use of incomplete data, in the recent obstetric literature. Stewart and her colleagues[12] published a report raising the suspicion that radiography in pregnancy led to an increased incidence of leukæmia in childhood. Further studies have not confirmed this contention.[13] Even so, this matter cannot yet be regarded as being finally settled, and one can understand the need for getting into print even a suspicion of such an important subject. One could only wish that the desire to publish urgently was always attended by such worthy motives.

"After this, therefore, because of this".—One can pick up almost any medical journal and be fairly confident of finding an example of this old chestnut. There was a recent paper which showed very nicely the relationship of smoking to the incidence of premature labour. Of course, this no more proves that smoking *causes* prematurity than that smoking causes cancer of the bronchus. It is interesting to speculate upon how posterity will view current thinking on this subject. After all, we view with amusement the reasoning of the ancient Romans who, noticing that they were more likely to contract malaria if they went out

on hot evenings, concluded that hot air must cause malaria.

The fallacy of many questions.—One can get a good deal of amusement out of this fallacy. The trick is to pose several questions at once in the hope of gaining recognition for a point which might otherwise be doubted. To illustrate, it is sometimes hard to find any obstetrician who will admit to the use of the somewhat dubious procedure of elective induction. Despite this, taken collectively, hospital records may reveal an increase in this practice. But it is interesting how often the truth slips out if you phrase the enquiry, "Have you noticed how often the cervix is found to be unripe when you go to perform an elective induction?" The medium of "many questions" can be useful in eliciting the status of the unmarried gynæcological patient. The direct question, "Are you a virgin?", is offensive and will not necessarily improve the doctor-patient relationship, but the technique of "Have you noticed any pain or bleeding after intercourse lately?" will often reveal information of great relevance and importance.

This section would not be complete without reference to some of the more common verbal fallacies.

Amphibology.—Ambiguity of grammatical structure can lead to confusion. In this paper, examples of this error are included. In the paragraph about Sir James Mackenzie, the phrase "he did a lot of his valuable early researches" is open to criticism since it may be taken to imply that his *later* researches were of no value, an obvious untruth. Again the obstetrician who writes, "I do not hesitate to rupture the membranes even if the head is not engaged" could be accused of sanctioning rupture of the membranes in an oblique lie, and it serves him right.

Accent.—A lot of damage can be caused by emphasizing the wrong word. Consider the sentence: "I recall several hospitals *in England* where the quality of the records made them very suitable for retrospective analysis." This could be interpreted as meaning that the hospital records in Canada were deplorable. One often encounters this fallacy in the department of faint praise. For example, "Dr. Blank is *technically* the finest surgeon in the city". The innuendo here may be that Dr. Blank is in fact a shocking diagnostician.

Figure of speech.—This consists of misinterpretation of a form of expression. The word "significant" is a common example. One frequently reads that the results of an experiment were "significant", but it is often doubtful if the writer means this in the statistical sense or otherwise.

6. *The final contemplation of the work done*

The conclusion of any research project should always deal with the assessment of the work in its broadest context. To return for the last time to our example, it must be obvious that merely to conclude that the method of treatment reduced the postpartum hæmorrhage rate would rather leave the reader up in the air. One would be bound to measure the advantages against any intercurrent disadvantages that may have arisen, say an increase in the rate of manual removal of the placenta or toxic reactions to the drugs employed. From the experience gained, one would also be expected to describe the circumstances in which it was felt that the method would be of value. In Canada, where few deliveries are conducted by midwives, it is doubtful that the method has any application. Lastly, one could hardly end by recommending such a routine and empirical method of treatment without referring to the fundamental need for seeking the cause of unexpected postpartum hæmorrhages.

SUMMARY AND CONCLUSIONS

This paper may be of interest to two main groups of doctors (separated by a somewhat arbitrary division): practising physicians and those having a particular interest in the conduct of clinical research. The busy practitioner is often the man who raises the questions that need to be answered. But having asked the question, he has to rely on others to provide the answer. What is new in medicine is not necessarily good. It is hoped that the principles outlined may help in the task of separating the wheat from the chaff.

For those engaged in clinical research, doubtless most of the material presented may be considered to be elementary. But if we are to judge from some of the communications appearing in the medical press, it would appear that even such fundamentals would bear repeating.

The subject of statistics in clinical research is mentioned but briefly and only in a particular example. It is not suggested that this represents a balanced view of the place of statistics in our work. Fleming did not need a mass of figures to demonstrate that penicillin was a valuable remedy, and there have been countless great discoveries in medicine which did not require statistical support. However, if Fleming were alive today and were to introduce penicillin to our present strains of staphylococci, it is possible that he would have to enlist the aid of statistical knowledge to prove his point. It is a rare clinician who commands a sufficient understanding of statistics to be self-sufficient, but this need not be important, provided the advice of the statistician is sought before designing the experiment and not afterward.

The conduct of clinical research is a responsible task. It is not possible that we will always be right whatever care we take. It is possible that by seeking high standards and understanding what these standards are we may be able to produce research of such quality as to bring new benefits to our patients.

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Sept. 15, 1959, vol. 81

THE CANADIAN MEDICAL ASSOCIATION
JOURNAL
LE JOURNAL DE
L'ASSOCIATION MÉDICALE CANADIENNE

published twice a month by
THE CANADIAN MEDICAL ASSOCIATION
Editor: S. S. B. GILDER, T.D., M.B., B.Sc.
Managing Editor: T. C. ROUTLEY, M.D., F.R.C.P.[C]
Assistant Editor: M. R. DUFRESNE, M.D.
Editorial Offices: 150 ST. GEORGE ST., TORONTO
(Information regarding contributions and advertising will be found on the second page following the reading material.)

CRISES IN THE FAMILY

It seems to be generally agreed that in western countries the stability of family life is not what it was in a less enlightened age. The causes of marital stress and strain are not however too well known, in spite of the fact that many so-called experts are prepared to pontificate in the press and give their prescriptions for connubial bliss.

The shaky foundation on which these prescriptions are based was clearly revealed at a meeting of the sections of psychiatry of the British and Canadian Medical Associations in Edinburgh this year, when Dr. H. V. Dicks of London, England and Dr. R. G. S. Arthurs of Toronto contributed short papers on psychological crises in family life. Dr. Dicks based his findings on a statistical study carried out at the Tavistock Clinic on the whole sample of married couples (157 couples) which passed through his unit between certain dates. This sample of cases in which marital disharmony had led to a need for psychiatric help was compared with a matched control sample of adequate size of "happy" marriages. Among the questions investigated were those of the relationship between the ages of the spouses and the duration of the marriage to its stability, the relationship to stability of socio-economic factors, the role of children in preserving marriage, and the relationship between marital stability and childhood history of the partners.

The study revealed no significant effect of relative ages of the two partners on the stability of a marriage, but it showed that on the average trouble had become acute some eight to nine years after the marriage. The critical period for a marriage appeared to be the fourth decade of life, for the age group 30 to 39 seemed to be the most popular for divorce and separation.

The study dispels the notion that freedom from want leads to a happy marriage, for such adverse factors as bad housing or poor economic status seemed to have no effect in disrupting marriage. Indeed there was some evidence that the concept of "love in a cottage" might have some scientific foundation, for some couples said that they were happier when they were struggling than later when they became financially secure. It is possible that a lack of the need to strive against adverse economic circumstances may lead to more tension in other respects. It is also interesting to note that none of the 157 couples involved in the study cited intellectual or cultural differences between the partners as a cause for disharmony. Nothing in the study suggested that a marriage is more stable because it has lasted longer; it would seem that the concept of a life-long effort to maintain a marriage in a state of stability is correct.

The one striking factor in the Tavistock Clinic sample was that no less than 239 out of 299 persons involved came from broken homes or disturbed homes in their childhood. Only 4.2% of the couples both came from a good home as against 54% in the series of happily married. This is a most strikingly significant finding, and emphasizes once more that persons who have had an unfortunate childhood are poor risks in marriage. It is commonly supposed that having children assists in the preservation of a marriage, but Dr. Dicks stressed that in the present series the number of children born was not significant. He also stressed the point that the persons involved showed few overt neurotic symptoms apart from their marital disharmony. In other words, as he aptly phrased it, the marriage may be the patient and not the man or the woman.

Lastly, another point made in this discussion was the significance of disturbances in role playing by the male and the female in the modern world. The alliance of an inferior and guilt-ridden male with a dominant woman does not make for marital harmony. This is a point which deserves further study, though it is doubtful whether the present trend among certain sections of our western civilization to a reversal of the traditional roles of male and female can be checked or modified by the medical profession.

Editorial Comments

MEDICAL SECRECY

Since Dr. Brouardel produced his textbook on medical secrecy in 1887, a voluminous literature has grown up throughout the world on this very difficult problem. In spite of this mass of scholarly writing, contributed not only by physicians but also by lawyers, philosophers, and even theologians, the subject remains in a delightfully vague state in many parts of the world. A Swiss lawyer, Egli, has recently discussed the problems involved in medical secrecy, and although much that he has to say is applicable mainly to Switzerland, he has certain general thoughts which are applicable to the practice of medicine in a setting elsewhere.

He points out that the main difficulty arises from the fact that while the medical profession in a country establishes a code designed to safeguard the confidences of the patient, the common law also may establish a code which runs counter to the former.

Egli makes the point that although the code of professional secrecy was in the first place instituted in the interests of the patient, it is also a powerful guarantee of the liberty of the medical profession. Remarking that in recent decades certain rights hitherto considered fundamental to the well-being of the individual have become abrogated more and more in favour of the collectivity, he urges organized medicine to consider the subject once more and to take steps to erect a rampart against this invasion of the individual's privacy. Indeed, so little do individuals think of their basic rights nowadays that many medical confidences are betrayed not by the physician but by the patient. He notes that in Europe there are two concepts of medical secrecy; in countries such as France, professional confidence is considered by tradition to be absolute and unbreakable, whereas in other countries it is only considered as relative. This means that in countries such as France, the patient has no right even to authorize his physician to divulge his confidences to a third party. In countries with the other type of legal climate—and this includes Switzerland and also the Anglo-Saxon countries—the patient may give his physician the right to disclose certain information obtained during professional practice.

In Switzerland, however, the physician has to be very careful about the nature of this permission, for unwarranted disclosure of professional confidences may lead to his being fined or imprisoned, and these legal sanctions may be taken not only against the physician but also against his helpers, his students or even his wife if she is working with him. This applies not only to medical matters but also to disclosure of any other facts which the physician may have learned while attending his patient. The most that the patient can do is to give the physician the right to communicate material to a third party; he cannot oblige the physician to do so. A point sometimes overlooked in this matter is that a complete medical history may contain confidential material on others besides the patient, such as his relatives. Obviously, obtaining permission from the patient does not give the physician the right to communicate such material.

The growing intrusion of governmental and other social insurance agencies into the practice of medicine has made it impossible to preserve the complete professional confidence which once existed as a matter of course. This is no reason, however, for forgetting about the matter altogether. Egli's paper reminds us that even where the law or insurance agencies are concerned, the doctor needs only to divulge as much as is strictly necessary for the smooth working of society. Thus, for example, the Swiss government has at last given in to the protests of the Swiss Medical Association and agreed that medical certificates and other reports passed across to the medical departments of the federal administration must be kept there and not passed around to other government departments. This concession suggests that there was never any real need to pass these documents around; as Egli points out, physicians should continue to watch out for unnecessary breaches of confidence, because such confidence is an integral part of professional liberty.

HELPING LITIGANTS IN SUITS AGAINST DOCTORS

In a recent letter to the editor of the *Lancet* (May 30, 1959), a layman states that when a person who thinks he has been harmed by a doctor tries to get evidence to support his claim, doctors from whom advice and help are sought tend to enter a conspiracy of silence which, by making it impossible to get expert testimony, effectively denies the complainant justice. The writer also says that members of the medical profession should be as willing to give evidence against each other as are the members of other professions. An editorial in the same issue discusses some reasons why doctors may be loath to provide such assistance, comments that more specific medical knowledge nowadays obviates the need for so much reticence, but says that there are still reasons why doctors perhaps may not feel as free as members of some other professions to testify against each other.

In Canada, particularly in Ontario, somewhat the same complaint has been heard recently. Members of the medical profession, as well as lay persons, have been saying that aggrieved patients are sometimes denied justice for lack of expert testimony. As a matter of fact, except in rare cases, this is probably not true. In Canada the medical profession is not plagued by nuisance suits and so doctors are not instinctively antagonistic to complainants seeking expert testimony that will ensure them legal redress. There are few plaintiffs with cases of any merit who have been unable to get expert medical testimony. It is probably true that patients with well-grounded complaints have no more difficulty in finding expert witnesses from among doctors than doctors whose work is good have in finding expert witnesses to testify to its adequacy.

The main deterrent in the majority of cases is the disinclination of a doctor to appear in malpractice actions as a witness for either defendant or plaintiff. Another difficulty is that, while medicine may have, and undoubtedly has, become more scientific, application of the science to the patient still demands much art as well as science, so that the distinction may be hard to draw between the well treated and the poorly treated patient.

Moreover, a doctor who is being blamed for refusing to provide expert testimony may have refused to act because he recognized, in the care of the patient, inherent difficulties unknown to the complainant. The doctor may also have recognized that the illness or damage from the injury was so severe and of such gravity that even a poor result was the best that could have been obtained by anyone.

This leaves a minority of cases where patients with just grievances, which a doctor can appreciate

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as valid, ask doctors to provide expert testimony which will be damaging to another doctor. What should the doctor do under these circumstances?

In the first place, the doctor should have it clearly in his own mind that he and his opinion are not for hire; it is true that he may be paid if his opinion is helpful to a plaintiff but this should not tempt him to reach an opinion that will ensure him the fee; he and his opinion are not for hire. The Code of Ethics says "the medical witness in Court should be actuated by a desire to assist the Court in arriving at a just decision and not merely to further the interests of the party on whose behalf he has been summoned." If there seem to be reasonable grounds for thinking that the patient is the victim of incompetent services the doctor should first obtain all the information available through the patient—this, of course, includes a carefully taken history and a searching examination—as well as any other relevant information; only after consideration of all the facts should an opinion be reached.

If this opinion, on a scientific basis, is unfavourable to the patient's claim the doctor should be candid; he should state his opinion and should refuse to testify for the patient. If on the other hand the opinion, on the same scientific basis, is favourable to the complainant, the doctor should remember that he ought not to deny justice to the patient and he should be willing to testify for him.

It is difficult for a doctor to resolve the conflict between his duty to be ethically correct, to refrain from making "adverse comment on treatment already given" and his broader duty as a citizen to assist a person wronged by a doctor to obtain legal redress. A doctor should be expected to recognize the circumstances where his greater duty is to aid the course of justice, but he should not be asked or expected to favour a plaintiff merely because the latter cannot understand why a result of treatment does not fulfil expectations.

LOOKING AFTER THE ADOLESCENT

Although Shakespeare maintained that there were seven ages of man, the ingenuity of the physicians has only succeeded in splitting human life into three ages so far. The first is of course the province of the pædiatrician and the last the domain of the gerontologist. What lies in between has so far been allotted to that majority of physicians who do not belong to either of these two specialties. However, recently it has been suggested that the adolescent deserves the care of a fourth type of physician, or at least should receive his medical care in a setting different from those allotted to children and adults respectively. There are of course difficulties in this age distribution, since no one can say exactly when adolescence begins and when it ends. Moreover, although the pædiatrician is and should be interested in his patients until they have passed the age of puberty, many general physicians and internists are greatly concerned with endocrine and other changes which may take place during this period.

The British Pædiatric Association has recently asked a committee to look into the problem of medical care of the adolescent, and this committee has furnished an interim report in which they define adolescence as the phase of intellectual, social, emotional and physical change through which the individual progresses in passing from childhood to maturity. This is a fairly elastic definition, since some individuals practically never mature at all. The committee does not wish to preserve this age group for the pædiatrician, but hopes that everyone concerned will take a hand in the care of adolescents, cheerfully rebutting any criticism of multiplicity of care.

One serious problem presented by this age group is connected with admission to hospital. Should they be admitted to wards with young children or with adults? The committee thinks that special beds for adolescents, on a basis of 10 to 20 for a population of 500,000 persons, should be provided but is not willing to go so far as to set up outpatient adolescent units like the one at the Children's Medical Center in Boston. However, they admit that it would be very interesting to try the experiment in some British centres of setting up clinics for adolescents, with the realization that most of the special problems involved would be psychological ones, and the clinics would be mainly psychiatric. We must at least be thankful that the committee does not recommend the establishment of a new class of specialist, the ephebologist, whose concern it would be to get everybody through this dangerous period of life with a minimum of mental and physical trauma. Looking back to a time before the teenager had been discovered, we wonder just how so many of us managed to get through without major scars. Or did we?

RESEARCH INTO AFFECTIVE STATES (INVOLUTIONAL MELANCHOLIA)

Every human being is capable of a broad spectrum of emotional experiences—and this capacity for experiencing life meaningfully is possible because of a feeling-tone mechanism which is woven into the fabric of the personality. A good deal of scientific information has accumulated since the beginning of the century, and given considerable insight into the psychological, neurological and endocrinological aspects of man's feeling or affective life. It has been possible to distinguish the pattern of homœostatic mechanisms which operate to maintain a balance in the dynamics of affective behaviour (recognizing the great variety of constitutionally determined variations in human reactivity which gives each individual his unique characteristic). And it has been possible to distinguish those who exhibit pathological disturbance of effect (i.e., where homœostatic mechanisms have failed the individual in maintaining satisfactory adaptation) and those who have affective disorders, with symptoms—usually of anxiety, excitement or depression accompanied by distressing ideation—reactive to current life experiences. But there is a large group

of affective disorders—also with symptoms of anxiety, excitement, depression, or elation—which develop under conditions of what appears to be little or minor stress. This group is considered to suffer from an endogenous affective disorder; that is, a disorder orginating within the biological organization of the organism.

The problem of endogenous psychiatric conditions has been under study in many centres for some time, but the etiology and pathology is still not clear. It is for this reason that a recent monograph by Dr. Ake Stenstedt of Stockholm* is of special interest. This monograph is devoted to an etiological, clinical and social study of endogenous depression in later life, with special reference to genetic factors.

In particular, the study deals with the syndrome of "involutional melancholia", a term which, as Dr. Stenstedt immediately points out, has been used freely but rather loosely. It becomes evident that its definition is somewhat unclear, but there is general agreement that this term refers to a depressive illness coming on in the later years of life. The author goes to some trouble to establish diagnostic criteria for involutional melancholia as a clinical entity, but, after perusal of the literature, he concludes that "there is no generally accepted opinion on the symptomatology of the disease". However, most authorities refer to involutional melancholia as an affective disorder characterized by depressive mood with anxiety or agitation (rarely with retardation), feelings of unreality, and delusional ideas of a hypochondriacal or nihilistic kind developing for the first time in the involutional period. Statistically, the illness occurs more commonly in women than men—in the ratio of 3:2. In women, the age range is between 40 and 55, and in men between 50 and 65. The syndrome tends to occur more frequently in persons of rigid, meticulous, overconscientious, obsessional personality.

Dr. Stenstedt's monograph was based on a study conducted under the ægis of the department of psychiatry of the University of Stockholm. The main object of this venture was to study the etiology of the syndrome, and Dr. Stenstedt's approach was to use the genetic method. He attempted to determine the risk of mental illness and mental abnormalities amongst the relatives of patients with involutional melancholia (patients designated in this way are called probands), and to subgroup the relatives according to etiologically relevant factors. The risks in the subgroups are then compared with each other and with the risks in the general population. The monograph details the method of investigation, the selection and analysis of the proband material, and the evaluation of morbidity risk (with respect to the affective disorder under study) in the general population, and provides a good deal of valuable reference material drawn from other workers. The study involved 307 probands with involutional melancholia (70 males and 237 females) and their sibs and parents—2282 persons in all—a prodigious undertaking, particularly in view of the meticulous attention to detail evident from the presentation of material in the monograph.

*Involutional Melancholia. Ake Stenstedt. 71 pp. Ejnar Munksgaard, Copenhagen, 1959.

The main points emerging from Dr. Stenstedt's study can be summarized as follows:

1. *Referable to the clinical material (probands) studied*

(a) Seventy-four per cent had only one depressive episode; 45% were considered to be pathological personalities; 61% developed depressive states reactive to psychogenic or other exogenous factor; 9% were women who developed a depressive state in connection with the menopause.

(b) Main symptoms noted were agitation, retardation, bizarre hypochondriacal and nihilistic delusions.

(c) The majority of the patients were either unmarried or divorced.

(d) Suicide was commoner in the patient group than in the general population.

2. *Referable to the relatives of probands*

The risk for mental disorder other than that of endogenous affective states was no greater than that in the general population.

No genetic connection seemed to exist between endogenous affective states and other types of mental diseases.

The study indicated that the risk of endogenous affective states amongst sibs and parents of probands was 6.1%. This compares with the figure of 6% reported by other workers doing genetic studies of this kind—and the figure of 3% for the general Swedish population (based on investigations by Fremming and Essen-Moller).

This monograph is an important contribution to psychiatric knowledge. It represents a merging of sound basic research with a penetrating clinical evaluation of a common and distressing psychiatric entity, and makes worth-while reading for those interested in psychiatric research. Basically, the study has revealed that hereditary factors play a significant part in the etiology of endogenous affective states. On the other hand, items such as the sex of the person, frequency or severity of depressive attacks, presence of pathological personality characteristics, somatic disease or unfavourable environmental conditions in childhood were not considered to be etiologically significant in involutional melancholia.

Dr. Stenstedt has made a significant contribution towards the understanding of affective disorders. This, together with research on a broad front, will probably lead to better understanding of the etiology and pathology of affective disturbance—and inevitably to improved methods of therapy.

A. MILLER

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Medical News in brief

CURRENT STATUS OF THERAPY IN RHEUMATIC FEVER

In a report to the Council on Drugs of the A.M.A., McEwen (*J. A. M. A.*, 170: 1056, 1959) states that prevention of rheumatic fever is best achieved by prevention of hæmolytic streptococcic infections or by prompt intensive treatment of an existing infection. Continuous prophylaxis is carried out with benzathine penicillin G (one intramuscular injection of 1,200,000 units every four weeks), with sulfadiazine or a multiple sulfonamide in doses of 500 mg. or 1 gram daily in a single dose or penicillin tablets (buffered soluble salt of penicillin G, or phenoxymethyl penicillin) 250,000 units by mouth twice daily. At present, the following rules are recommended for continuous prophylaxis. It should be given to any child who has ever had an attack of rheumatic fever or who has heart disease due to rheumatic fever, and to an adult after a recent attack of rheumatic fever or if rheumatic heart disease is present. Added protection in the form of higher doses of antibiotic or sulfonamide should be provided during procedures such as dental extraction, major or minor surgical operations or other situations where bacteria may enter the blood stream. Strict diagnostic criteria should be used to decide whether or not continuous prophylaxis should be given to a patient, and the "modified Jones criteria" are recommended for this.

The relative values of salicylates and corticosteroids are discussed and the conclusions of the "Cooperative Clinical Trial" are quoted. The regimen used by investigators in Santiago, Chile (Mortimer, Vaisman, Rammelkamp *et al.*) is described and its value discussed. It is possible that intensive antibiotic therapy of this type may be preferable in the case of the rheumatic attack which has already begun. This would particularly apply if corticosteroid therapy were used in that period, as high antibiotic coverage might prevent the spread of infection, which may be encouraged by the steroids. In the present state of our knowledge, two conclusions with regard to rheumatic fever can be drawn. (1) Corticosteroid therapy cannot control the underlying, unknown mechanism of rheumatic fever and does not prevent the progession of permanent valvular damage. Rheumatic polyarthritis and fever can be suppressed with equal rapidity and greater safety by means of salicylates. (2) Group A hæmolytic streptococci are known to incite rheumatic fever and should be eliminated early in the course of this disease; new infection by these micro-organisms should be prevented.

RUPTURED ANEURYSM OF THE INFERIOR THYROID ARTERY ASSOCIATED WITH PARALYSIS OF THE VOCAL CORD

A rare cause of paralysis of the vocal cord is reported by Doumanian, Soule and Ellis of the Mayo Clinic (*Proc. Staff Meet. Mayo Clin.*, 34: 303, 1959). A small aneurysm of the right inferior thyroid artery in a 60-year-old farmer was found to have ruptured. This had caused hoarseness of seven weeks' duration preceded by a sudden onset of pain in the right side of the neck and some swelling of the submandibular region. The inferior thyroid artery was removed at operation and the aneurysm measuring approximately 5 mm. in diameter and revealing a rent in the intima was demonstrated. Although neoplasms in the neck are the most frequent cause of paralysis of the larynx, cardiovascular disease is second in importance in its etiology and this case is an example of one of the rare vascular causes.

TUBERCULOSIS COMPLICATED BY PREGNANCY

Opinions are conflicting on the damaging effects of pregnancy on a woman with active tuberculosis, yet the problem is not rare, for in a recent series of antenatal patients 1% were found to have active tuberculosis. Flanagan and Hensler from an air force base in California (*J. A. M. A.*, 170: 783, 1959) have reviewed all the cases in which active pulmonary tuberculosis and pregnancy coexisted over a two-year period. They compared the fate of these 22 patients with 40 non-pregnant tuberculous controls. In both series, approximately 60% of patients had moderately or far advanced tuberculosis with cavitation, and positive results of bacteriological tests had been obtained in 60 to 75%. Only one person in each group had previously received drug therapy for tuberculosis, and only three or four had received any treatment for the condition.

Results were assessed in the two groups as regards the rate of stabilization (evaluated on the evidence of the roentgenogram), sputum conversion, and cavity closure. No significant difference as regards progress between the two groups was discernible by any of these criteria, and there was no evidence that pregnancy affected adversely or otherwise the prognosis in tuberculosis, provided that the disease received the the same treatment whether the patient was pregnant or not. Obstetrical results in the pregnant group were excellent; 21 had normal deliveries of healthy babies at term.

RUPTURE OF THE ACHILLES TENDON

Between 1940 and 1957, no fewer than 92 patients were treated for subcutaneous rupture of the Achilles tendon in the Department of Surgery of the Karolinska Hospital, Stockholm. In analyzing this series in a monograph (*Acta chir. scandinav.*, Supp. 239, 1959), Arner and Lindholm state that 86 of their 92 patients underwent operation while the others were treated conservatively. Most of the patients were men, and the mean age for the whole series was 38.5 years. The authors consider that the rupture is probably always total and usually occurs between 2 and 6 cm. above the insertion. Subcutaneous rupture cannot be induced by indirect violence if the tendon tissue is healthy. It is suggested that degenerative changes in some of these cases were due to previous violent participation in sport. Tendon suture gives excellent results. Conservative treatment will lead to healing with lengthening of the tendon and may cause considerable disability.

(Continued on advertising page 63)

NEW DRUGS

This listing of new products is based on information received from Dean F. N. Hughes, Faculty of Pharmacy, University of Toronto, and the *Canadian Pharmaceutical Journal*, to whom we owe thanks.

Diethylproprion: TENUATE, Merrell

Description.—Each tablet contains 25 mg. of Tenuate (diethylproprion), an anorexic agent without central nervous stimulation.

Indications.—In control of obesity.

Administration.—One tablet 3 times a day *one hour* before meals and one in mid-evening if desired.

How supplied.—100, 1000.

Fibrinolysin: ACTASE, Ortho

Description.—Human fibrinolysin for dissolution of intravenous clots.

Indications.—Venous thrombosis, thrombophlebitis, phlebothrombosis, pulmonary embolism.

Administration.—Best to institute treatment within five days of the thrombotic incident. Reconstitute contents of 50,000 unit vial with 10 c.c. Water for injection U.S.P., add to 250 c.c. of fluid for intravenous infusion such as Dextrose Injection 5% U.S.P. Infuse intravenously over a period of two hours. Repeat according to specific directions observing precautions.

Contraindications.—Any hæmorrhagic diathesis, major liver dysfunction, hypofibrinogenæmia.

Should be used within three hours of reconstitution.

How supplied.—Vials of 50,000 Fibrinolytic Units. Store at 0° to 10° C.

Phenformin: DBI (Pr), Arlington-Funk

Description.—Each scored tablet provides 25 mg. phenformin (N'beta-phenethyl-biguanide HCl), oral hypoglycæmic agent.

Indications.—Alone, often controls stable adult diabetics; with insulin, may improve regulation of brittle diabetes in both juveniles and adults; reduces insulin requirement by 50% or more in many cases. Has been effective in insulin-resistant cases and in primary tolbutamide and chlorpropamide failures.

Administration.—Follow detailed instructions.

How supplied.—100.

Trypsin: ORENZYME, Merrell

Description.—Each enteric coated tablet contains: trypsin 68%, chymotrypsin 30%, ribonuclease 2%, equivalent to proteolytic activity of 20 mg. crystalline trypsin.

Indications.—For resolution of inflammation and œdema, alone in mild inflammatory conditions, and as an adjunct to parenteral and/or buccal trypsin in a number of clinical conditions, e.g., contusions, crush injuries, fractures, sprains, phlebitis, etc.

Administration.—Initially 2 tablets 4 times daily. As maintenance therapy or as an adjunct one tablet 3 or 4 times daily.

How supplied.—48.

OPHTHALMIC PREPARATION

Spiramycine: ROVAMYCINE Ophthalmic Ointment (Pr), Poulenc

Description.—1% spiramycine base in a greasy excipient which allows rapid penetration of the antibiotic.

Indications.—Eyelid infections (burns, styes, blepharitis, abscesses), mucopurulent and purulent conjunctivitis; ulcerous keratitis of infectious origin; trachomas; preoperative and postoperative treatment in ocular surgery.

Administration.—Apply locally, 2 to 4 times per day, depending on the severity of the case.

How supplied.—Tubes of 4 g.

MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films. The films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

PSYCHOLOGY AND PSYCHIATRY

Schizophrenia: Simple-type Deteriorated—1951; Sound; B & W; 11 minutes.

Produced by the National Film Board of Canada for the Department of National Health and Welfare. Technical advisers: George E. Reed, M.D. and Heinz Lehmann, M.D., Verdun Protestant Hospital, Montreal, Que.; Charles G. Stogdill, M.D., Department of National Health and Welfare. *Mental Symptoms series, No. 1.*

Description.—An instructional-record film, presenting a characteristic clinical picture of chronic simple schizophrenia. A psychiatrist reviews the characteristic symptoms and then interviews a female patient.

Appraisal (1952): A good demonstration of deteriorated simple schizophrenia. Should be very useful in demonstrating the condition to medical students and nurses where an actual clinical presentation is difficult, too time-consuming or undesirable for other reasons. Suitable also for general medical audiences and professional groups such as psychiatric social workers and psychologists. *Unsuitable for non-professional audiences.*

Availability: National Medical & Biological Film Library ($1.00). Purchase from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.O.

Symptoms in Schizophrenia—1938; Silent; B & W; 17 minutes.

Produced by J. D. Page, University of Rochester.

Description: A record-instructional film, illustrating certain of the symptoms most commonly found in chronic schizophrenia (i.e., those which can be shown by silent motion picture photography). Several examples of the four clinical groups are presented.

Appraisal (1945): Recommended for medical students and interns, and students in psychiatric nursing and abnormal psychology. There should be an indication that the bizarre behaviour shown by certain patients is not necessarily "meaningless"—that it has a significance as far as the patient is concerned. Up-to-date, with the rider that we seem to have passed beyond the point where patients' faces require covering with a mask. *Unsuitable for non-professional audiences.*

Availability.—National Medical & Biological Film Library ($1.50). Purchase from the Psychological Cinema Register, Pennsylvania State University, State College, Pa.

Unconscious Motivation—1949; Sound; B & W; 39 minutes.

Produced by Dr. Lester F. Beck, Department of Psychology, University of Oregon.

Description: An instructional-record film, demonstrating the action of unconscious motivation as initiated by hypnosis, and showing some of the standard psychological techniques used to detect and release such motives. Reactions of the subjects throughout the film are spontaneous and unrehearsed.

Appraisal (1950).—An unusually good film, serving to portray in a simple way something which all except those thoroughly versed in psychotherapy find difficult to grasp—namely, the relationship between trauma and symptom. Recommended for all professional medical audiences—specialist, practitioner, student and nurse—as well as for university classes in psychology. Suitable for interested scientific and lay groups, provided a competent authority is present to lead discussion and answer questions.

Available: National Medical & Biological Film Library ($6.00). Purchase from Association Films Inc., 35 West 45th Street, New York 19, N.Y.

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PARASITOLOGY

The Life Cycle of the Malaria Parasite—1951; Sound; Colour; 22 minutes.

Produced by W. M. Larkins Studio and Film Producers Guild, for Imperial Chemical Industries Limited. Technical Adviser: Col. H. E. Shortt, C.I.E., M.D., Ch.B., D.Sc., D.T.M.& H., I.M.S(Ret.), F.R.S.

Description.—An instructional film, illustrating the complete life cycle of the malaria parasite. Consists entirely of animated drawings in colour.

Appraisal (1952).—One of the best films of its type. An effective illustration of the life histories. Should be a useful film for classes concerned with tropical diseases or studying parasitology. The drawings are most realistic, the presentation is clear and the commentary accurate and to the point. Recommended for medical students. Suitable for other professional and scientific audiences. Inappropriate for the lay public.

Availability.—National Medical and Biological Film Library ($3.00). For purchase apply to the Publicity Department, Imperial Chemical (Pharmaceuticals) Limited, Fulshaw Hall, Wilmslow, Manchester, England.

Trypanosoma Brucei—193-; Silent; B & W; 5 minutes.

Produced at the Pasteur Institute.

Description.—This silent film with French subtitles presents a micro-cinematographic record of some aspects of the morphology and behaviour of *Trypanosoma brucei.*

Appraisal (1956).—Strictly a record film which, in the hands of a microbiologist, may be effective as a demonstration of the behaviour of *Trypanosoma brucei.* Has little value as an instructional or teaching film for students, because of its brevity and the scarcity of subtitles. Technical content is accurate and acceptable. Suitable for any interested medical or scientific audience.

Availability.—National Medical and Biological Film Library ($1.00). For purchase apply to the Pasteur Institute, Paris, France.

PUBLIC HEALTH

Taken for Granted—1948; Sound; B & W; 18 minutes.

Produced by World Wide Pictures for the Middlesex County Council.

Description.—A factual instructional-training film, portraying the operation of a large sewage disposal plant serving a metropolitan area—the sewage disposal system of the western part of Middlesex County, at Mogden, England, serving 1,250,000 people.

Appraisal (1949).—A very good factual film, well presented. Useful for undergraduate and graduate classes in public health as a general introduction to the subject. Also suitable for the lay public, particularly in those cases where the subject is before the community as an undertaking, and where a sanitary engineer is present to discuss the subject.

Availability.—National Medical and Biological Film Library ($2.00). Purchase from Canadian Film Institute, 142 Sparks Street, Ottawa 4, Ontario.

See also the *National Health Film Library Catalogue,* listing films dealing with many aspects of the broad field of health and hygiene. Copies may be obtained on request from the Information and Promotion Division, National Film Board of Canada, P.O. Box 6100, Montreal 3, Que.

RADIOLOGY

Radiography of the Lumbar Spine—1947; Sound; Colour; 23 minutes.

Produced by the Medical Arts Department, Christie Street Hospital, Department of Veterans Affairs, Toronto, Ontario. Technical Advisers: Department of Radiology, Christie Street Hospital (Dr. Desmond T. Burke, Chief Radiologist).

Description.—An instructional-training film, demonstrating on a live model correct procedures for obtaining good diagnostic radiographs of the lumbar spine.

Appraisal (1949).—A clear and emphatic demonstration of optimum procedures and of certain points which are not always as carefully considered as they should be. Recommended for radiologists and radiological technicians. Inappropriate for other audiences.

Availability.—National Medical and Biological Film Library ($4.00). Department of Radiology, Sunnybrook Hospital, Toronto 12, Ontario (loan). In the U.S.A.: Contemporary Films, Inc., 13 East 37th Street, New York 16, N.Y. (rental). For purchase apply to Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, Que.

FILM ON CROSS INFECTIONS IN HOSPITALS

A film dealing with the problem of cross infections in hospitals has been produced by the American Medical Association, the American College of Surgeons and the American Hospital Association, with the support of Johnson & Johnson of New Brunswick, New Jersey. It was produced under the supervision of Dr. Carl Walter, Associate Clinical Professor of Surgery, Harvard Medical School, and a committee representing the three organizations.

The 30-minute film, in sound and colour, is designed to educate hospital personnel concerning the many avenues by which infection can be spread throughout a hospital, and utilizes the staphylococcus by way of illustration and as an example of one of the most important phases of the problem. It will lay the groundwork for the delineation of the problems relating to specific fields in a series of shorter films to follow.

The film was shown at the annual meeting of the A.M.A. in Atlantic City on June 8-12, at the Assembly of the W.M.A. in September, and will be shown later at professional gatherings throughout the world.

FILMSTRIPS

Three filmstrips of scientific exhibits at medical conventions, photographed and put on film by Lakeside Laboratories, are now available for teaching purposes. They are as follows:

"Bone Marrow Patterns in Infancy and Childhood", by Drs. Thomas L. Rider, Paul R. Patterson and Simon Propp of Albany (N.Y.) Medical College and Albany Hospital. This exhibit was presented originally at the 1958 American Academy of Pediatrics meeting in New York City.

A combined strip featuring "Cancer Cells in the Circulating Blood" and "Hematopoietic Response to Iron Dextran Therapy". The cancer cell exhibit was prepared by Dr. Alvin L. Watne and associates of the University of Illinois College of Medicine and was presented at the 1958 convention of the American Medical Association in San Francisco. The second segment of the filmstrip is based on the exhibit prepared by Drs. Herbert S. Bowman and Rosemarie J. Tursky of Harrisburg (Pa.) Hospital which was presented at the American College of Physicians' 1958 meeting at Atlantic City, N.Y.

The third filmstrip in this series features the work of Dr. Roy F. Goddard and associates of Lovelace Foundation. This project, a review of pædiatric bronchopulmonary disorders, is also from the A.M.A. convention.

Running time for each strip is 15-20 minutes.

The filmstrips are available to all medical colleges and county, state and regional medical societies. They may be obtained free of charge from Helen Martin, Executive Secretary, "Exhibits-On-Film," Lakeside Laboratories, Inc., 1707 East North, Milwaukee 1, Wisconsin.

REVIEW ARTICLE

THE BRAIN AND THE POISON*

J. OLSZEWSKI, M.D., Ph.D.,
Saskatoon, Sask.

INTOXICATIONS supply only an insignificant fraction of routine neuropathological material. However, their study has great theoretical importance since they may serve as models of neurological diseases which are now classified as degenerative, metabolic, or simply "of unknown etiology". We know that some of these diseases are caused by specific disorders of metabolism and we may assume that others have a similar, though at present unknown, etiology. Many diseases belonging to this general group are hereditary. This further substantiates the hypothesis of their metabolic nature, since it is now accepted that the genes exercise their influence on the organism by regulating enzymes concerned with various steps in metabolic processes.

One of the most striking features of metabolic disorders is the precise and selective localization of the lesions which they produce. A similar predilection for a specific localization of cerebral lesions is shown by many poisons, and information gained while studying their effects may have a direct bearing on the understanding of naturally occurring degenerative diseases of the central nervous system. It is the purpose of this presentation to give a few examples of the central nervous system intoxications which illustrate these points, and to draw conclusions from these examples, pertaining to the general approach to research in this field of neuropathology.

In discussing the mode of action of chemicals on the nervous system and the problem of selective toxicity it is appropriate to introduce and explain the concept of pathoclisis. This term was invented by C. and O. Vogt[1]† as a name for a local selective tissue vulnerability due to physico-chemical properties of the tissue involved. They observed that lesions of the nervous system due to systemic diseases are limited to morphological units, and they postulated that this localization is due to physico-chemical, sub-microscopic differences in the organization of the tissue. Further, they postulated that the presence of morphological dissimilarities indicates some sub-microscopic differences. For many reasons, the theory of pathoclisis did not gain as wide a recognition and acceptance as it deserves. Perhaps the main reason for this is that it only indicates in general terms the road to understanding of the problem of localization, without actually explaining individual instances. The other reason is that it was put forward at a time when biochemistry with enzymology had not been incorporated into the everyday thinking of pathologists, and the discipline of neurochemistry was recognized by a few specialists only. The story of pathoclisis is a good example of a scientific theory which was too advanced for the time when it was introduced and therefore was not appreciated by its contemporaries. A scientific theory must stimulate further research and must be amenable to experimental techniques, available at the time, otherwise it becomes forgotten or is considered a useless piece of mental exercise.

It is interesting to see how the present-day development of biochemistry in general, and neurochemistry in particular, has given us evidence confirming the Vogt's concept of pathoclisis. A good example of this is the lesion of the hippocampus, characterized by loss of cells in sector H_1, the so-called Sommer sector. It is well known that H_1 is particularly vulnerable in a wide variety of pathological conditions, of which anoxia is the commonest. The Vogts postulated that this vulnerability is caused by a specific physico-chemical property of the neuronal cells of sector H_1, which is not shared by other sectors of the hippocampus, and which is reflected in a different histological appearance of these cells. Against this hypothesis, the school of Spielmeyer argued that the mechanics of the circulation are responsible for this selective vulnerability. They pointed out that sector H_1 is supplied by terminal branches of the arterial tree and is therefore more exposed to malnutrition, when this blood supply becomes diminished. We cannot go here into details of the prolonged and animated discussion which followed. Though the Vogts themselves, and some of their pupils, were convinced that they were right, no direct evidence of any physico-chemical difference which could be correlated with the differential pathological vulnerability was available. Recently, however, MacLean[2] has shown that single injections of 3-acetylpyridine produce a degeneration of sector H_1 in mice. Almost at the same time Fleischhauer and Horstmann[3] showed that zinc is present in sector H_1 of the hippocampus, but not in other sections. Whether these two phenomena are related as cause and effect is not known at present, but the observation of the varying zinc content is of particular interest, since this metal is known to be a component of alcohol dehydrogenase, whose co-enzyme is diphosphopyridine nucleotide. This latter compound contains nicotinamide which acts as a hydrogen carrier, and 3-acetylpyridine is a known nicotinamide antimetabolite. Certainly we are still far away from a complete understanding of the pathogenetic relationships involved, even in this single and apparently simple example, but perhaps we are now on the way to a solution of this problem. These thoughts may be followed by more speculative ideas expressed

*From the Laboratory of Experimental Neuropathology, Department of Pathology, College of Medicine, University of Saskatchewan. Based on a talk at the meeting of the Neurological Sciences Club, February 2, 1959, Saskatoon, Sask.

†Professor Oscar Vogt died in July 1959, at the age of 89, in his home in Neustadt, Germany. The scientific world lost a great scholar, and many of us a dear friend. May this article serve as a tribute to his memory from a student who owes so much to his teaching.

recently by MacLean.[2] He quotes: (a) the observation of Vallee that, in cirrhosis of the liver, there may be a disturbance of zinc metabolism, and (b) this author's concept that this may be the result of damage to alcohol dehydrogenase which contains zinc, by repeated heavy doses of alcohol. Now, we must remember that zinc is particularly abundant in certain areas of the hippocampus and that modern theory links this structure with memory, and that in Korsakov's syndrome a high intake of alcohol and memory disturbance are two outstanding characteristics. The ideas expressed by MacLean may be right or wrong, but certainly further investigation in this direction will be interesting and fruitful.

Another example of selective vulnerability which cannot be explained other than on the basis of physico-chemical specificity—that is, pathoclisis—is offered by the study of the toxicity of various quinoline derivatives. Schmidt and Schmidt[4] and Richter,[5] while investigating the toxicity of antimalarial drugs, studied a number of quinoline derivatives. They found that long-continued administration of "plasmosid" to monkeys produced localized degenerative changes in several brain stem nuclei, among them the nuclei for the eye muscles, nuclei of cranial nerves VII and VIII and nuclei gracilis and cuneatus. However, when the chemical structure of the compound was changed slightly by introducing a methyl group into the side-chain the toxicity disappeared. This toxicity could be restored by attaching to the molecule of the inactive compound the molecule of sulfadiazine, which by itself is not neurotoxic. Not only did the toxicity reappear, but it was now directed at different nuclei like the hypoglossal and the facial, whereas some of the nuclei affected before remained intact.

It is difficult to explain these phenomena on any other basis than pathoclisis, though the nature of this affinity and the mechanisms involved remain at present completely obscure. The histological alterations produced by quinoline compounds are similar to those found in thiamine deficiency. Denny-Brown expressed the opinion that these substances may have an anti-thiamine effect, but to my knowledge this hypothesis has not been studied.

It is of interest that other quinoline compounds have toxic effects on the central nervous system, which differ from the above not only in their localization but also in speed of action. Some isoquinolines, also called berberis alkaloids, produce a flaccid paralysis in rabbits. This develops immediately after—or even during—the injection. Animals allowed to survive two to five days show a spongy degeneration of the cervical and thoracic cord with liquefaction necrosis at the lumbo-sacral level. Here again a slight change in chemical structure—introduction of hydroxyethyl instead of methyl groups—renders the substance inactive.

Another interesting example of selective toxicity, which is also striking from the point of view of the histological changes produced, is intoxication by certain organic compounds of tin. That these compounds are toxic, not only for experimental animals but also for man, has been proved by the tragic mass intoxication that occurred in France in 1954 when 110 persons died from ingestion of diethyl tin chloride.[6] This compound was present in pills put on the market as a drug for treatment of furunculosis. The belief that tin was of benefit in skin infections was widespread in France and apparently originated from an unconfirmed report that furunculosis was uncommon among workers handling tin. This tragedy would not have happened if the literature on the toxicity of tin had been searched adequately. Indeed, in 1881, White reported that triethyl tin was highly toxic to various animals with predominant neurological involvement. As with other metals, tin has varying properties depending on the form in which it is administered. Metallic tin and inorganic tin compounds have only slight toxicity, whereas tin attached to alkyl groups becomes intensely toxic. This has been attributed to changes in solubility, but it is quite possible that other factors may be of significance.

Magee, Stoner and Barnes[7] studied the clinical picture and pathological changes found in rats suffering from acute and chronic intoxication by organic tin compounds. The first interesting observation was the difference between effects of diethyl tin and triethyl tin. The former is toxic, but only if introduced directly into the stomach; in addition it does not produce characteristic neuropathological changes and BAL is an effective antagonist. The latter is not antagonized by BAL and causes characteristic neuropathological changes with a corresponding clinical picture. It acts either if mixed with the diet or if injected intraperitoneally. Chronic intoxication by triethyl tin sulphate causes progressive paralysis of the hindlegs, and later of the forelegs, which is reversible if administration of the drug is stopped. Pathological changes are confined to the white matter of the whole nervous system and consist of spongy transformation, which is interpreted by the authors as interstitial œdema. A characteristic feature is the absence of an inflammatory reaction, and the ability to return to a normal appearance once the administration of the toxin is stopped. The nervous tissue is grossly œdematous, and chemical investigations show a significant increase in water content without changes in other constituents of the tissue. The studies of vascular permeability were most interesting, since they failed to disclose any changes in the usual properties of the blood-brain barrier. This latter observation is of special significance since it is an example of cerebral œdema resulting not from vascular damage, but most likely from changes in the osmotic properties of the tissue. This mechanism of cerebral œdema, which may be responsible for increased intracranial pressure

in certain conditions, should receive more attention in the future.

Thus in the toxicity of the alkyl-tin compound we have another example of selective toxicity which can well be explained in terms of the Vogts' pathoclisis. These attempt to understand the mechanism underlying the toxic effects of diethyl and triethyl compounds have been linked with the work of Aldridge and Cremer,[8] who studied the biochemical properties of these two compounds and their influence on metabolism *in vitro*. They found that there was a difference in their actions, diethyl tin chloride inhibiting alpha-keto acid oxidases, whereas triethyl tin sulphate inhibited phosphorylation processes associated with oxidation. However, it seems that it would be an unjustified simplification to consider this property of triethyl tin as the cause of its selective and specific action, since other substances which cause inhibition of phosphorylation processes, like 2,4-dinitrophenol, do not produce similar effects. In addition, there is no evidence that triethyl tin accumulates in the nervous tissue in general and in the white matter in particular, and therefore there is no explanation for the selective action of this substance which affects a metabolic step common to all the tissues of the body.

The list of examples of selective toxicity by compounds known to have a potent general effect on metabolism can be greatly lengthened, particularly by adding various types of antimetabolites. Though we seem to understand the basic mechanisms by which these compounds exert their toxic effects, we fail to comprehend two cardinal phenomena related to their action. The first is the selective nature of the damage to part of the organism despite a general derangement of metabolism which is thought to be identical in all organs and tissues. The second is the differences in the toxic effects and the localization of the lesions, depending on the use of different antimetabolites, which according to present knowledge act against the same metabolite. For instance, 3-acetylpyridine and 6-amino-nicotinamide are both antimetabolites of nicotinic acid, and though both are toxic, only the second produces degenerative changes in the anterior horn cells and brain stem nuclei, as shown by Sternberg and Philips.[9]

Similarly, Hicks[10] has shown that lesions which seem to be related to anoxia localize in different sites depending on the method used to produce the disordered intracellular respiration. Thus, for example, the hippocampus is damaged in insulin hypoglycæmia but is spared in asphyxia due to nitrogen inhalation, which on the other hand damages the substantia nigra. Both these structures remain intact in fluoracetate poisoning, though this substance affects the cerebral cortex. These findings indicate beyond doubt that in addition to anoxia other factors must be active during the development of these lesions.

All the observations described above show the inadequacy of either a purely morphological or a purely biochemical approach. The problem of localization is the central problem of neurology and the key to better understanding of the function of the central nervous system. This problem will not be solved by any unilateral approach. A mere registration of morphological changes, important as it may be for recognition of clinical entities, is not going to teach us much more about the pathogenesis of the disease processes. The study of disorders of metabolism conducted *in vitro* on homogenized preparations, in which all morphological relationships have been destroyed, is pitifully inadequate to deal with an organ as highly organized as the central nervous system. The morphologists and biochemists must combine their efforts if further progress in the understanding of pathological processes and normal functions of the nervous system is to be achieved.

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MEDICO-LEGAL

THE DOCTOR AS A WITNESS*

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THE TOPIC assigned to me is the position of a doctor appearing in Court as an independent expert witness. This, of course, is a very big subject, and in the time at my disposal I shall be able only to outline briefly some of the important points.

In the first place it should be understood that while the Courts always respect medical opinions, they are not binding upon the Court or jury who are free to draw their own inferences from the facts, and accept or reject the statements of doctors as they see fit. As Viscount Simon once observed, a medical expert's opinion "is admissible in evidence solely to fill up the gap due to the tribunal's inability to draw a proper *technical* conclusion from the facts".[1] The final decision always rests with the Court.

Although he may refer to them while testifying, a doctor should carefully re-examine his report, notes and other relevant documents before the trial. It is also important that he should have a pre-trial conference with the attorney who is to call him and

*Presented at the Sectional Meeting of the American College of Surgeons at the Queen Elizabeth Hotel, Montreal, April 8, 1959.

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review the evidence he proposes to give. At the same time he may make any suggestions that may occur to him as to questions that might usefully be put to the opposing medical witnesses in cross-examination.

The attorney should open his examination by asking the doctor to state his qualifications, and it is important (since he is there as an expert) that these should be given fully. There are different methods of doing this. One is to tell the witness beforehand that when he is asked for his qualifications, he must give them all freely and voluntarily without prompting. In practice, however, doctors are notoriously hesitant about doing this. In any event, some authorities (e.g. Clark Sellers) feel that a full answer is unwise since it might give the Court the impression that the witness is "preening his peacock feathers".[2] These authorities feel that it is preferable to obtain the required information by a series of prepared questions. Personally I have made a habit of saying at the outset, "Doctor, will you please lay aside your natural modesty and tell His Lordship and the jury all your qualifications!" This usually produces a smile, and is at least partially effective in bringing forth a satisfactory answer. The remaining qualifications must be extracted one by one.

When the evidence is conflicting (as it usually is) there is an almost irresistible tendency to take sides. The doctor, however, should be careful not to assume the role of advocate in the witness box. If, in effect, he pleads the case of the party who called him—and this is not uncommon—the Court is usually quick to realize that he is biased, and his evidence loses much of its effect. In one case (cited in Gradwohl's "Legal Medicine"),[3] a physician, after entering the witness box and before he had been asked any questions, said, "Before I answer any question I want to know what side I am testifying for"! Needless to say, this is an extreme case!

Many cases (especially those in which there is conflicting evidence as to disability) develop into "battles of experts". This consumes a great deal of time and money, and is to be avoided when possible. In this connection I should refer to the practice in force in the Supreme Court of the State of New York. Under that system panels were set up consisting of neutral outstanding physicians and surgeons in various specialized branches of medicine. These experts are available at the Court's request to examine plaintiffs in bodily injury cases, report their findings, and if necessary testify in cases in which the medical evidence is conflicting. A case may be referred for an impartial opinion at the pre-trial conference under New York procedure, and the judge may make the order for such a reference without necessarily obtaining the consent of the attorneys. The judge does not know the names of the doctors, but only what specialists are available. Their names are kept confidential so that there will be no opportunity or temptation for a lawyer to seek the services of any particular doctor. When the case is referred to the experts, a date is set for a resumed pre-trial conference. Statistics show that this procedure has resulted in many settlements. It has also lightened considerably the heavy back-log of cases awaiting trial. Another plan which has been employed by some of our Montreal judges in cases of conflicting medical evidence is to suggest to the doctors for both sides that they confer together before testifying in order to determine whether they can reach some agreement as to disability, etc.

Sometimes medical evidence is given which is unethical from a legal and/or medical standpoint. It is interesting to note that some 12 years ago a Committee was appointed by the President of the Minnesota State Medical Association to study and attempt to correct serious situations of this kind. In cases of a flagrant character, the Committee submits a report and a transcript of the evidence to the State Board of Medical Examiners. This Board has judiciary power to suspend or revoke the offending physician's licence.

The questions asked in examination-in-chief, i.e. by the lawyer calling the doctor as a witness, must not as a general rule be leading. In other words, they must not suggest the answer that the lawyer hopes to receive. In cross-examination, on the other hand, the opposing attorney may ask leading questions, and may therefore suggest things to the witness, e.g. that the evidence he has given on a certain point was inaccurate.

It is important, especially during cross-examination, to listen carefully to the questions, and to be sure that they are fully understood before replying. If a question is not clear (and many are not) the witness should request an explanation. Moreover, a doctor (like any other witness) should answer only the questions put to him. To volunteer unrequired information usually opens new doors, sometimes with unfortunate consequences.

Sometimes there is no cross-examination, either because the opposing attorney feels that no harm has been done, or because he does not wish to take the risk of making matters worse. He may then be content to forego his right to cross-examination, and to rely upon the evidence of his own medical witnesses. In other instances the attorney may ask only one or two questions of a kind that involves no risk. A classic example of this was Clarence Darrow's cross-examination of the prosecution's chief medical witness in the celebrated *Massey* case in Honolulu. That witness had been brought from the United States to testify, and it was generally expected that he would be subjected to a long and gruelling cross-examination. But Darrow's only questions were these: *Question:* Did you enjoy your trip from Los Angeles, Doctor? *Answer:* Yes. *Question:* Are you being paid for testifying in this case? *Answer:* Yes, I am.[4]

A doctor should stand firm on the evidence he has given, but if a new point arises on which he is uncertain, he should not hesitate to answer that he does not know. He may be referred to opinions of textbook writers, and is quite free to say that he disagrees with them if he sees fit. But he should not be surprised if the attorney appears to know something about medicine and questions him on views expressed in recent and current issues of medical journals. The fact is that most lawyers accustomed to dealing with medical witnesses make a point of studying the particular subject matter under the guidance of a specialist.[5] This often involves reading portions of books and journals, and sometimes the inspection of apparatus to see how it functions.

Sometimes a doctor leaves the witness box feeling that his evidence has not been shaken but has actually been strengthened by the cross-examination; and that may well be so. For the truth is that while this kind of examination is the advocate's most powerful weapon, it is a dangerous one which, if improperly handled, does more harm than good. Cross-examination of ex-

pert witnesses, such as doctors, requires special skill and should be undertaken only by experienced trial lawyers.

When the cross-examination has been completed, the attorney who originally called the witness may re-examine if necessary. The purpose of this is to deal with any new points that may have been brought out in cross-examination, and to have the doctor explain any of his answers that require explanation.

Although it may go against the grain the doctor should try to avoid technical terms, and to speak in language intelligible to laymen. But apparently medical witnesses find this rule difficult to follow. Not long ago, for example, a Montreal newspaper reporting on a case of alleged criminal abortion stated that the evidence "became so technical that time had to be taken while the jury, the lawyers and the presiding judge were straightened out by the doctors who rephrased their testimony in language understandable to laymen."[6] Unfortunately, the same sort of situation arises too often.

Although in his report a doctor may have expressed his opinion that an accident victim was malingering, it is not as a rule good practice to use that word in Court. Experience has shown that a blunt statement that the plaintiff is a malingerer may antagonize the jury. It is preferable for the doctor to state that he made a thorough examination of the case, that there were many complaints of many things, but that no physical signs could be found. In many cases he may truthfully say that there is no evidence of incapacity and that any feeling of inability the plaintiff may have would be overcome by work, and in any event would disappear as soon as the lawsuit ended.

It should be remembered that as a general rule hearsay evidence is inadmissible. Suppose, for example, that a doctor who examined the plaintiff when he was admitted to hospital is asked to describe the plaintiff's injuries. So far so good: but if the doctor then proceeded to state the opinion given by the radiologist on an x-ray examination of the same patient, that would be hearsay and subject to objection. The proper person to give that evidence is the radiologist.[7] There are, however, exceptions to the hearsay rule, two of which are of special importance to doctors. First: a dying declaration is admissible in cases of murder and manslaughter, provided the declaration was made in full belief of approaching death with an abandonment of all hope of life.[8] Secondly: declarations by persons as to their bodily or mental feelings are admissible when those feelings are material to be proved. Thus, it is common for a doctor testifying in a bodily injury case to describe the plaintiff's symptoms as he related them at the time of the medical examination. The statements must, however, be restricted to symptoms: they must not be in the nature of a version as to how and by whom the symptoms were caused.[9] For instance, if after describing the symptoms the doctor went one step further and related what the plaintiff had told him as to the cause of his injury (e.g. that a motorist was driving too fast), that evidence would be hearsay and accordingly illegal.

A party who engages a doctor as an expert witness is, of course, responsible for the doctor's charges. These will include fees for consultations, preparation of a report and attendance at the trial. The biggest of these items is likely to be for the Court attendance, even if the witness was detained no longer than was necessary for him to give his evidence. In most instances only a comparatively small proportion of the fee will be taxable, i.e. capable of inclusion in the bill of costs which is usually payable by the losing party. Litigants who complain of what they consider to be excessive fees sometimes fail to appreciate that a serious responsibility rests upon a doctor called upon to testify as an expert, and that the effect of his evidence may represent a difference of several thousands of dollars in the outcome of the case.

In malpractice cases the defence usually relies principally upon the evidence of independent medical experts. It is of great importance in my opinion that these experts should be retained and consulted at the outset of the case and, in any event, before the defence is filed.[10] Too often they are engaged only after the written pleadings have been completed, and sometimes just before trial. It may then be discovered that they are not prepared to support one or more important allegations in the defence, and the attorney may feel obliged to amend it at the last moment. This is a situation to be avoided if possible.

In all cases the doctor appearing as an expert witness should be prepared to give reasons for the opinion he expresses in Court. For example, to state that a plaintiff in an accident case is likely to suffer a permanent incapacity of 15% is not of much use unless the doctor is able and prepared to state how he reached that conclusion. And when he appears as a witness for the plaintiff, he should be able to establish a direct connection between the accident and the injury of which the plaintiff complains. This is important, because indirect or remote damages are not legally recoverable.

Finally, it should be emphasized that when a doctor is summoned to Court by subpœna, the summons should never be disregarded. Failure to comply with a subpœna is punishable by fine and even by imprisonment for contempt.[11] In many cases, of course, the attorney communicates with the doctor before trial, and tells him when he will be needed. The subpœna is then served as a matter of course, but the witness is not obliged to attend until notified by the attorney to do so. In some instances this may be several days after the date mentioned on the subpœna. But if no such arrangement has been made and the doctor finds that for some valid reason he is unable to comply with the summons, he should immediately telephone the lawyer responsible for issuing it and explain the situation. A subpœna may be in the form of a *duces tecum* ordering a witness to bring certain things to Court, e.g. a case record or an x-ray film. Particulars of the material required should be plainly stated on the subpœna. If the order is not entirely clear the doctor should communicate with the attorney who issued it and request an explanation.

FOOTNOTES AND REFERENCES

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2. In his chapter in R. B. H. Gradwohl's "Legal Medicine", 1954, p. 1000.
3. *Op. cit.* fn. 2 at p. 1006.
4. Irving Stone, "Clarence Darrow for the Defence" (1941).
5. For practical examples of the use of an attorney's medical knowledge in cross-examination see W. C. J. Meredith, "Malpractice Liability of Doctors and Hospitals", 1956 (The Carswell Co. Ltd., Toronto), pp. 49-50.
6. *Montreal Star*, December 17, 1954.
7. However, hearsay evidence of this kind quite frequently goes unchallenged; e.g. if the parties were agreed on the x-ray findings there would be no object in raising an objection.
8. R. W. Baker, "The Hearsay Rule" (1950), p. 91.
9. Phipson on Evidence, 9th ed., p. 80.
10. As to consultations with experts and preparation of pleadings, see Meredith, *op. cit.*, fn. 5 at p. 54.
11. Article 303, Quebec Code of Civil Procedure.

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THE JOINT B.M.A. - C.M.A. MEETING, EDINBURGH, JULY 1959

SCIENTIFIC PROGRAM*

The Editor wishes to thank the British Medical Journal *editorial staff and reporters for their kind collaboration in procuring this material.*

SECTION OF ANAESTHETICS
WEDNESDAY, JULY 22

R. A. Gordon (Toronto) described obstetrical anæsthesia in the Toronto General Hospital. Agents and techniques had changed during the past seven years, during which time almost 25,000 obstetrical anæsthetics had been given. In 1957 there were no maternal deaths, and the corrected fetal mortality rate was 19 per 1000. For vaginal deliveries, nitrous oxide and oxygen, with or without trichlorethylene, accounted for 50% of the anæsthetics. Local analgesia, and in particular lumbar epidural block, was used in a further 40%. Spinal analgesia was rarely used for Cæsarean section, having been replaced by epidural block. When general anæsthesia was used, intubation was considered unnecessary as a routine. The trend towards epidural block was justified by the results, only seven cases of aspiration of vomitus, none fatal, having been recorded during the period under review.

H. H. Pinkerton (Glasgow) discussed "a sense of proportion," with particular reference to training in anæsthetics. A wide and thorough training could yet lack a sense of proportion, and fundamentals might be overlooked. Orthodoxy had earned a high place for British medicine, but this did not prevent employment of improved means to achieve improved ends. However, only when the patient benefited were the means justified. Skilled anæsthesia was an advantage to surgeon and patient, but robbed the general practitioner of experience. Hypotension was a valuable technique in some circumstances, but the postoperative complication rate could be as high as 1 in 31. The introduction of halothane (Fluothane) had restored something of the "art of anæsthesia", but the employment of a novelty as a routine must be regarded as a retrograde step. In a responsible specialty such as anæsthesia, each "advance" must be viewed in its proper perspective. The glamorous techniques of extracorporeal circulation, hypothermia, hypotension, etc., were not necessarily applicable to the ordinary patient. Trainees must assess these methods properly, and eschew sensationalism, having been drilled first in fundamentals.

D. Matheson (Vancouver) spoke on epidural anæsthesia for lumbo-spinal fusion and laminectomy. The results of using epidural block, subarachnoid block and general anæsthesia were compared, with special reference to blood loss. With laminectomy as the sole operative procedure, there was little to choose between these methods of anæsthesia. When laminectomy was accompanied by spinal fusion, a markedly lower blood loss occurred under epidural block. Dr. Matheson stated that the blood loss increased disproportionately if the operation time exceeded two hours, and was aggravated by superimposed general anæsthesia. The greatest blood loss was encountered under nitrous oxide, oxygen and halothane, but this was also related to the duration of the operation. The results were not influenced by the posture of the patient.

Epidural block with 2% lignocaine and 1:300,000 adrenaline (average dose 20 ml. injected at L2-3 or L3-4) was considered an ideal method of anæsthesia for operations on the lumbar spine, except in the presence of new growths and infection.

R. Woolmer (London) read a paper on new methods for the analysis of respired gases. He said that it was desirable for the anæsthetist to know the composition of an inspired gas mixture presented to a patient. Ideally, there should be continuous measurement of all components. Separate analysis of the inspired and expired gas mixtures would provide additional information about uptake and excretion of volatile anæsthetics. To do this, physical or physico-chemical methods have advantages, including the actuation of a recording device. The analysis of a complex gas mixture requires three stages: separation of components, their identification and quantitative measurement. Gas chromatography might be developed to make continuous recording possible, and thus eliminate the guesswork which could no longer be accepted in clinical anæsthesia. Although gas chromatography could perform the three steps required, a single measurement took approximately ten minutes. This time must be reduced if the method was to become of practical value in the operating theatre.

In speaking about sensory thresholds in light anæsthesia, J. G. Robson (Montreal) referred to John Snow's "second stage of narcotism". This was characterized by amnesia and analgesia. A similar state could be caused by the inhalation of 40% nitrous oxide and 60% oxygen. Mixtures of nitrous oxide and oxygen inhaled by volunteers caused a reduction in the rate of learning simple problems and also reduced the rate at which they were forgotten. The pattern of memory impairment was similar to that encountered in subjects with temporal lobe lesions. These memory tests, and response to perception and sense of time, were influenced by the concentration of nitrous oxide inhaled. Since variations as small as 5% in the gas mixture could vary the time estimate, it was suggested that this test might be used as a form of bio-assay.

SECTION OF CHILD HEALTH
PSYCHOSES IN INFANCY AND CHILDHOOD
FRIDAY, JULY 24

K. Cameron (London) emphasized that juvenile psychosis followed a well-defined pattern. Historical terms such as dementia infantilis, dementia precocissima or infantile autism all represented intermediate forms of a wider syndrome. Early developmental history was rarely normal, though the child was usually

not backward chronologically. Symptoms usually started at 2-3 years, sometimes precipitated by an episode of emotional or physical trauma such as accident or burn. The fully developed picture was that of withdrawal, regression, alteration in mentality, diminution of effort and emotional response, and presence of patterns of thinking, feeling and actions derived from inner thoughts. Subsequent progress could be apparent recovery with or without later adult schizoid trends, partial recovery with residual brain damage, or deterioration into subsequent adult schizophrenia or even progressive dementia. It could be almost impossible to distinguish between a defective and a deteriorated schizophrenic, but the latter usually had a history of normality with periods of development and regression.

W. A. Hawke (Toronto) spoke on constitutional and environmental factors in etiology. Two recent Toronto studies, on 50 and 40 autistic children respectively, had both shown a significant tendency towards schizophrenic disturbances in the families. Parents were often very intelligent, the average I.Q. being over 120, but 80-90% were classed as moderately or severely neurotic or themselves schizoid. They were often singularly unsuccessful in community or family life. Only 25% could form an adequate relationship with therapist or child. Rejection by their autistic child often led to further withdrawal on the part of parents. Little could be done to influence the constitutional factor, and efforts had to be directed to improve the relationship between child and parents. Sometimes placement in a foster home or institution was unavoidable.

F. H. Stone (Glasgow) agreed that the results of known therapy of juvenile psychosis were poor but said that treatment should include support and explanation for parents, an optional therapeutic milieu for the child with individual psychotherapy where necessary, special educational facilities, and temporary use of sedatives and tranquillizers. Such needs could probably best be met by day psychiatric hospitals, especially in areas such as Glasgow where cases were increasing and beds were scarce. Great care was necessary in choosing staff, who must be highly trained, stable and sensitive, and show special understanding of psychotic mental processes such as symbolism and disturbance of body image. Attendance of children should be daily. Continued parental co-operation was essential but often difficult; guilt feelings must be relieved and warning given of danger of regressions during treatment and after change of environment. Where in-patient therapy was essential, prior establishment of parent-child rapport was of great help but some relapsed acutely and had to be sent home.

Mildred Pott (London) stressed that any plan of therapy for psychotic children must take into account stress and strain on the family and especially on normal siblings. Community care would not be suitable for some. A total assessment should be undertaken on every case by a comprehensive team including general practitioner, pædiatrician, neurologist, psychiatrist, psychologist and psychiatric social worker. Small residential units with special educational facilities would be optional for some cases, provided close contact was maintained with the family as part of treatment of both child and parents. Long-term responsibility for all forms of therapy should be in the hands of one psychiatrist or team, for continuity of treatment and keeping of complete records for much-needed research.

SECTION OF CHEST DISEASES
FRIDAY, JULY 24

Sarcoidosis

A. Anglin (Toronto) read a paper on sarcoidosis, a systemic disease affecting most organs of the body, which had been given a variety of names. The etiology was uncertain, but its common association with tuberculosis suggested a tuberculous origin. It was sometimes possible to trace a gradual change from sarcoidosis to tuberculosis. Tubercle bacilli were not found in sarcoid lesions and injection of sarcoid tissue into animals did not produce tuberculosis. A geographical survey of sarcoidosis in the U.S.A. had revealed an endemic zone along the eastern coast, coinciding with the distribution of pine forests. There seemed to be a definite link between pine pollen and sarcoidosis. Pine pollen had certain chemical similarity to the tubercle bacillus, and, when injected, the pollen could produce a sarcoid-like reaction. Pine pollen had been found in the sputum of some patients with sarcoidosis. Histologically sarcoidosis was characterized by epithelioid tubercles with little or no necrosis. Young adults were usually affected. The illness ran a chronic course and tended to remit spontaneously. Constitutional disturbances were mild. Increase in serum alkaline phosphatase probably indicated liver involvement. Monocytosis and eosinophilia were not uncommon. Radiological changes could be found in the bones of the hands and feet. Chest radiographs showed bronchial gland enlargement and changes in the lung parenchyma. In histological confirmation of the diagnosis, scalene node biopsy had proved valuable. It had recently been shown that the negative tuberculin test commonly found in sarcoidosis often changed to a positive test when patients were given steroid treatment. This might prove to be a valuable diagnostic test. Steroids provided the only satisfactory form of treatment for sarcoidosis.

J. W. Crofton (Edinburgh) said that he had been unable to confirm the association of pine forests with sarcoidosis in Edinburgh where most patients were town dwellers. It was interesting that American Negroes often developed sarcoidosis whereas African Negroes apparently did not. The incidence of sarcoidosis might reflect local medical interest in the disease.

Smoking and Lung Cancer

C. R. Lowe (Birmingham) summarized the facts relating to the controversy about the association between smoking and lung cancer. There was an undeniable statistical link between cigarette smoking and bronchial carcinoma. The incidence of lung cancer was very much greater in heavy smokers than in non-smokers. Figures from 16 countries had shown a rise in incidence of lung cancer following closely the increased consumption of cigarettes 20 years previously. The ratio of male to female deaths from bronchial carcinoma was closely related to their smoking habits. This was true for squamous and undifferentiated carcinoma, and not for adeno-carcinoma when the sex incidence was equal. It was in the interpretation of these facts that differences of opinion had arisen. It might be argued that it was lung cancer that caused people to smoke. Since we were dealing with a situation in human biology and not with a proposition of logic, the question resolved itself into one not of

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possibilities but of probabilities. The suggestion that some precancerous state caused an irritation inducing a desire to smoke could be dismissed. It was also possible that bronchogenic carcinoma and smoking were related through a common cause, for example an individual genotype. Thus a person might inherit a predisposition both to lung cancer and to cigarette smoking. There was evidence that personality traits had some bearing on smoking habits, and it was likely that the genotype was important in cancer of the lung. There was, however, no evidence whatever to suggest that there was a genotype which exhibited both proneness to lung cancer and a desire to smoke. On the other hand there was a great weight of collateral evidence to support the hypothesis that cigarette smoking was a direct cause of lung cancer. Unfortunately the subject was approached with bias. If the evidence did not relate to a drug marketed by a powerful and wealthy industry, and which provided the British government with a revenue from taxes more than sufficient to meet the cost of the National Health Service, it would already have been accepted as convincing enough to warrant public action.

Bronchiectasis

R. J. M. McCormack (Edinburgh) surveyed the present position of the surgical treatment of bronchiectasis in the light of experience from 252 consecutive patients treated by resection in Edinburgh. Claims had been made that antibiotics had replaced surgery in the management of bronchiectasis, but this was not true. Operative mortaility was low. There had been no deaths in the last 120 patients undergoing operation. Postoperative complications had become rare. Three-quarters of the patients treated by resection were able to return to a full life without respiratory symptoms. In only about one-tenth of the patients had the results been disappointing. Failure of surgical treatment was usually due to coincidental chronic bronchitis. Recurrent bronchiectasis had been found in 26 patients, but critical review of the preoperative bronchograms had often shown that the extent of bronchial dilation had been greater than originally suspected. Surgical resection was the best treatment of bronchiectasis provided the disease was sufficiently localized to allow adequate resection and provided the patient did not suffer from chronic bronchitis as well.

Cough and Cancer

J. D. Adamson (Winnipeg) described an investigation into the incidence of bronchial carcinoma in patients with a chronic cough. It had been asserted that almost any sort of bronchial irritation would give rise to bronchial carcinoma, although, if this were so, it seemed strange that carcinoma was increasing in incidence while lung infections were decreasing. To test the validity of the suggestion an investigation had been carried out by comparing the case histories of 500 Canadian pensioners dying from bronchial carcinoma with an equal number of controls of similar age. The accuracy of the data seemed certain since all cases had dependable case histories going back for at least 10 years, together with periodic radiographs. All the diagnoses had been confirmed at autopsy. The results showed quite clearly that chronic cough was no more common in patients with bronchial carcinoma than in those dying from other causes, while there was no difference between the two groups in either the intensity or duration of cough. Results showed conclusively that patients with chronic cough were not more prone to bronchial carcinoma than their fellows.

SECTION OF GENERAL PRACTICE
THURSDAY, JULY 23

Dr. J. McKenty (Winnipeg) began the session by giving an account of the College of General Practice in Canada, whose main activities so far had been organizing an annual scientific convention where members met one another and heard scientific papers, in organizing the Rockefeller survey of Canadian general practice, and in advancing the postgraduate education of general practitioners by methods such as sending teams of consultants to outlying areas and using tape recordings. McKenty felt that they had much to learn from their British colleagues, especially as regards general-practitioner research.

H. Gibson Hall (Toronto) had studied the early features of hypertension in his practice over a period of 26 years. He recognized four periods of stability of blood pressure. From the ages of 15 to 19 the blood pressure tended to be unstable and labile; from 20 to 54 there was a period of stability, followed by a labile phase from 55 to 62; and finally in old age the blood pressure was again stable. These facts applied to men as well as women. He had noted that in old age there was a tendency for the blood pressure to fall by 8-10%. He had observed 514 patients with a family history of hypertension and had noted a progressive rise in blood pressure after the period of stability from 20-54. In 173 other persons without this positive family history there had been no rise in blood pressure. He had found that obesity was definitely related to an unstable and rising blood pressure at a younger age. Emotional factors were often a cause of a rising blood pressure which tended to persist. A case history was quoted of a man with a very strong family history of hypertension. His blood pressure had been within normal limits until his forties. The first rise had been noted when one brother died from cerebral hæmorrhage, and a few years later a much greater rise was associated with the death of a second brother from the same cause. The patient himself eventually died from a cerebrovascular accident.

I. H. Stokoe (Edinburgh), speaking on hypertension in the elderly, said that it was important because some 50% of deaths in the aged are from cardiovascular diseases, and because of the increasing proportion of the elderly in the community. The question of a figure for a "normal" blood pressure was a difficult one. His own criterion was 120 mm. Hg plus half the age, for those aged 65-90 years.

The common form of hypertension in the elderly was the systolic variety, which increased with age, but fell after the age of 80. As a rule symptoms were slight and often related to anxiety, but in a few hypertensives stress was associated with disorder of the heart, kidneys, and cerebral circulation. The prognosis was good, as the condition was thought to be a compensatory mechanism to maintain an ade-

quate circulation by overcoming the loss of elasticity and increasing rigidity of the larger arteries. Management consisted in advising moderation in all things. A thorough initial examination was important, as was the maintenance of an optimistic outlook to encourage and reassure the patient.

Lord Amulree (London) considered that "geriatrics" should be a label applied not to "old" persons, but only to those elderly sick with social and economic problems. These problems were four in number: (1) loneliness; (2) neglect, leading to dirt and squalor; (3) lack of domestic help; and (4) lack of food: we know little of the food needs of the elderly, but malnutrition in them is still appreciable.

All these problems made it difficult for the general practitioner to deal with the individual elderly sick person. He would require help. Although the home was the best place for the elderly, beds must be available for the acute case, social as well as medical. The risks of hospitalization in the elderly were listed as death, irreversible confusion, complications, and loss of independence. A hospital with a geriatric service would provide, in addition to beds, an out-patient service, domiciliary visits to assess the home situation, and co-operation with local authority services. Provision of sufficient district nurses, health visitors, and daily meals on wheels would do much to help the elderly live an independent life with the general practitioner in charge.

C. J. Houston (Saskatchewan) described the work of a general practitioner on the Canadian prairies and his tasks in evaluating the physical, psychological, social and economic factors in the patients' illnesses. He considered that 90% of illnesses can be managed by the general practitioner alone in his own practice. The *physical* factor in disease is easily evaluated by him in a well-equipped modern office, where he carries out physical examinations and urine and blood tests. The *psychological* factor was difficult to evaluate, in spite of his long and detailed personal knowledge of his patients. On the prairies a commonsense approach was most suitable. *Social* factors occupied a small role in the cause of sickness. They could produce a delay in resolution. Generally, on the prairies there were fewer artificial social values and much greater sense of personal responsibility. The *economic* factors in Saskatchewan, a land of plenty, were less important than ever before. He thought that in his practice there was less morbidity and less malingering than in Britain where the medical bill was paid by a third party. He concluded by stating that under the type of service existing in Saskatchewan there was the lowest infant and maternal mortality in the world, the best cancer detection service, and the lowest tuberculosis rate.

R. Scott (Edinburgh) reported socio-medical research studies carried out in the General Practice Unit of Edinburgh University. He stressed the quantitative loads of physical, psychological, social and economic factors in his lower social class practices. There was a rise in the number of doctor-patient consultations with age, more apparent in women than in men. A survey of housing standards showed that there was a close correlation between standards and the age of the patients. A fall in standards occurred as age advanced, and many of the elderly lived alone and in isolation. The importance of socio-economic and human relationship factors was shown in the high proportion of cases (over 25%) that required this form of social therapy when compared with the more usual techniques of prescribing medicines, surgery, and certification. Emotional instability was noted in 9% of all consultations and here the peak levels were noted in women between 25 and 50. In the future the requirements for a comprehensive and integrated service in general practice would require consideration of the increasing numbers of the aged in the population and the relative proportions of the elderly to the younger age groups who had to care and look after them.

SECTION OF HISTORY OF MEDICINE
WEDNESDAY, JULY 22

This section, inaugurated at the Edinburgh Meeting in 1927 by Dr. John D. Comrie, was, on the present occasion, appropriately held in the Hall of the Royal Medical Society (founded 1737).

Instruction in the History of Medicine

The first paper, which dealt with "Proposals for a reform of the course of instruction in the History of Medicine", by L. F. G. Sennewald (St. Thomas, Ontario), was read, in the writer's absence owing to ill-health, by L. G. Stevenson (Montreal). The paper was a plea for the improved training of medical historians, and for a greater place to be assigned to the subject in the medical curriculum. The history of medicine should be treated as part of the history of civilization, and stress should be laid upon the importance of high ethical standards and upon the varying attitudes to disease, the transition from the magico-religious to the experimental, as the ages unfolded. The cult of great doctors was not desirable, as this laid too much stress upon genius and chance. The course should be in the third year of medical study or later, and it should be voluntary with no examination. The teacher should be a trained historian as well as an experienced doctor.

Phases in Medical Education

A wider view was advocated in the next paper, entitled "The varying phases of medical education", by H. E. Rawlinson (Edmonton). He said that the practical aspect of medicine was the main factor which continually stimulates and rejuvenates its progress. The teaching of medicine had developed from mere craftsmanship to a more formal and planned instruction, passing through the period of philosophy and humanism toward the scientific and experimental approach, with emphasis upon research at the present day. Each phase, as it appeared, was apt to be overemphasized, but the practicality and urgency of the medical problems restored the balance. There was still a tendency to underrate and even neglect the technical aspect of medicine, on the ground that a university is not a technical school, and this attitude was injurious, as it might even lead to a separation of medical teaching from the universities, as happened in past times. Fortunately the practical nature of the most urgent problems of medicine help to redress the balance.

(Continued on page 512)

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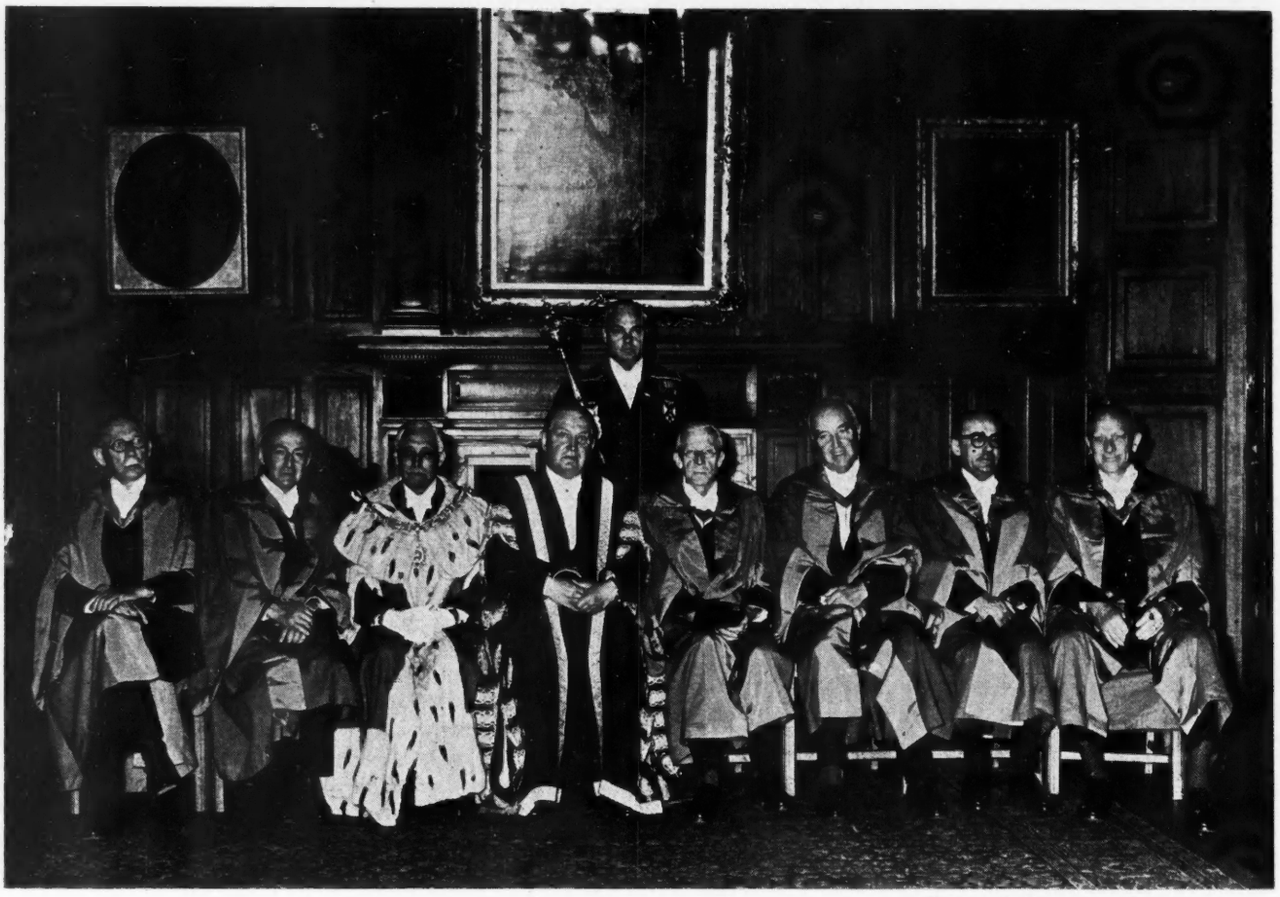

Edinburgh Evening Dispatch

The new honorary graduates who received the degree of Doctor of Laws in the University of Edinburgh on July 21, photographed with the Lord Provost of Edinburgh and the Principal of the University. Left to right: Dr. Angus Macrae, Sir Arthur Thomson, Lord Provost Sir Ian Johnson-Gilbert, Sir Edward Appleton, Lord Adrian, Dr. C. H. Best, Dr. Renaud Lemieux and Dr. Wilder Penfield.

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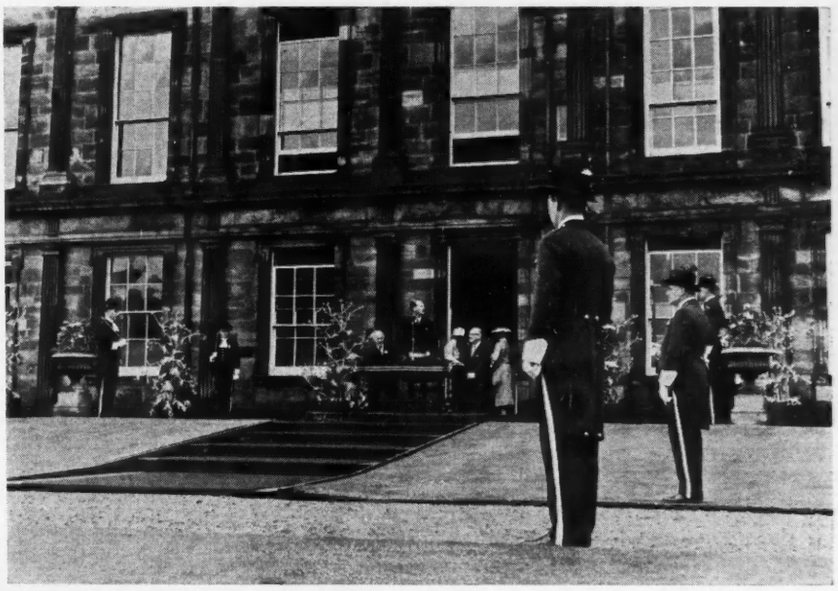
Lord Adrian addresses the Adjourned Annual General Meeting of the B.M.A. in Usher Hall on Monday night, July 20.



The Duke of Hamilton, Hereditary Keeper of the Royal Palace of Holyrood House, welcomes guests to the garden party. Seated at the table are Sir Arthur Thomson and Dr. E. Kirk Lyon. Protecting the party are the constables of Holyrood House. Adding to the decor are some of the giant thistles grown at the back of the palace.

Members of the two associations leaving St. Giles' Cathedral after the official Protestant service on Sunday, July 19. This group is headed by Sir Arthur Thomson, President of the B.M.A., and Dr. E. Kirk Lyon, Deputy to the C.M.A. President, followed by Dr. Arthur Beauchamp, Chairman of the B.M.A. representative body, and Dr. Norman Gosse, Chairman of the C.M.A. Council, followed in turn by Dr. S. Wand, Chairman of the B.M.A. Council and Dr. Murray Douglas, C.M.A. President-Elect, and by the two Treasurers, Dr. L. D. Callander and Dr. G. W. Halpenny.

This picture shows about half of the company assembled at dinner in the Waverley Market on Tuesday, July 21.

All photographs on this page by Film Surveys Ltd.

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(Continued from page 509)

The Anti-Scurvy Club

An eloquent and colourful account of "The Anti-Scurvy Club, 1606 A.D." was given by A. L. Murphy (Halifax, N.S.). The scene was set when Samuel de Champlain, with his friends the Baron of Poutrincourt and Marc Lescarbot arrived in Nova Scotia to establish, at Port Royal in Acadie, the first colony in the New World. Discovering very soon from bitter experience that scurvy would be their greatest enemy, Champlain planned its prevention. He believed that poor food was the main cause, with loneliness and lack of fresh air as contributory causes. To counteract all three, he founded a club which he called "The Order of the Good Time". It did much to allay the scourge, and before anything was known of vitamins, his efforts were to a great extent successful. The Club came to an end, but was revived centuries later, and still lives as the oldest social club in America.

At the close of the meeting, on the Nova Scotia soil of a corner of Edinburgh Castle esplanade, Dr. Murphy presented Dr. Douglas J. Guthrie with a certificate of membership of "The Order of the Good Time".

Sir Charles Bell

E. W. Walls (London) gave an account of the life and work of the famous surgeon, Sir Charles Bell, who, born and educated in Edinburgh, went to London in 1804 to succeed the Hunters in the teaching of anatomy at the Great Windmill Street School. Bell became surgeon to the Middlesex Hospital and was the prime mover in the founding of its medical school. He conducted important researches on the nervous system for which he is so justly famed, and finally returned to Edinburgh as professor of surgery six years before his death. Bell's name is remembered eponymously in Bell's palsy, Bell's sign, the nerve of Bell and the Bell-Magendie law. His productivity was enormous and, being an artist of ability, he illustrated his own books.

Douglas of the Pouch

An anatomist whose achievement is less familiar than that of Bell was James Douglas, the pupil and assistant of William Hunter, whose work was described in a paper entitled "Douglas of the pouch", by K. Bryn Thomas (Reading). Thomas said that many of his facts regarding Douglas were derived from unpublished manuscripts in the Hunterian Museum at Glasgow. Like William Hunter, James Douglas combined the practice of obstetrics with the teaching of anatomy, and he published in 1707 the first teaching handbook in English, besides describing the line, the fold, the ligament, and the peritoneal pouch, each of which bore his name. He also made an important contribution to lithotomy, and he became a Fellow of the Royal Society in 1706.

Notable Members of the Royal Medical Society

W. A. Alexander (Edinburgh) dealt with "Some notable members of the Royal Medical Society". Originally constituted in 1737 by a small group of medical students, including William Cullen and John Fothergill, it is now in its 222nd session, and it has the distinction, unique among undergraduate societies, of possessing a Royal Charter, dated 1779.

During the first half of the 19th century a number of Canadian-born students joined the Society, the first being John Stevenson (1818), one of the original teachers at the Montreal Medical Institution, which became the McGill faculty. It is also interesting to record that the two founders of the B.M.A. and C.M.A., Charles Hastings and James Sewell, were members of the Society. Hastings was a president in 1815-16.

On the membership roll of the Society are many famous men such as Oliver Goldsmith, 1753, Peter Roget, 1796, and Charles Darwin, 1828. John Morgan and Benjamin Rush were members, as also were Astley Cooper, Charles Bell, Richard Bright, Thomas Addison, James Young Simpson, Joseph Lister, and a host of others. Well might Sir William Osler remark, in proposing the toast of the Society at its annual dinner in 1907, "I doubt if there is any other Society in the world, except, perhaps, the Royal Society of London, with such a Roll of Honour."

SECTION OF PREVENTIVE AND SOCIAL MEDICINE

AFTERCARE OF THE HOSPITAL PATIENT

WEDNESDAY, JULY 22

Hospital and Community

T. Ferguson (Glasgow) gave an account of an investigation based primarily on an unselected series of 705 men discharged from the general medical wards of four acute hospitals. The facts were disappointing. Britain was lamentably short of convalescent accommodation designed to restore capacity for work and bridge the wide gap between hospital ward and everyday life, and effective organized aftercare was only in its infancy so far as common major illnesses were concerned. It badly needed development if the work of the hospital was not to be speedily undone. More must be done to help the family doctor in his struggle to keep the patient on his feet and more to encourage the patient to follow a way of life satisfying to him and within his compass.

Progress after Hospital Treatment

R. W. F. Harnett (Dundee) reported a study similar to Professor Ferguson's in which 300 male and 100 female patients were visited one, three and twelve months after discharge from hospital; a final visit at two years was planned. One object was to demonstrate the effect on the subsequent progress of a patient of his medical management and also to assess his co-operation, insight and understanding. It seemed that where co-operation was lacking, 80% of patients had relapses. There was evidence that insight assumed some importance, particularly in patients with alimentary and cardiovascular diseases. Management rather than insight appeared to play a greater role in the progress of patients in the respiratory group. A more adequate explanation of the disease process, the limitations it imposed and, in particular, the use and purpose of the therapy recommended would have made treatment more effective.

Aftercare of the Elderly

I. M. Richardson (Aberdeen) suggested that there was a real need for an aftercare case conference committee in every sizeable hospital, especially where elderly patients were cared for. There were four key people involved: the hospital consultant, the hospital almoner, the family doctor, and the local authority social worker (who might be a public health nurse). In Aberdeen it had been found beneficial for the senior surgeon to lend his prestige to rehabilitation, but where, as in Aberdeen, there was 5% unemployment, rehabilitation was an economic problem first and a medical problem only second.

Aftercare of the Mental Patient

Preliminary findings were presented by J. H. F. Brotherston (Edinburgh) of an inquiry carried out in collaboration with three mental hospitals. All patients aged between 16 and 64 who had been discharged during an eight-month period were visited by a psychiatric social worker between one and two years later. Over a quarter of the patients had to be re-admitted to mental hospital one or more times in the interval since discharge. About a quarter were receiving further psychiatric out-patient treatment or were judged to be in need of treatment either as out-patients or in-patients. About one in six of the patients had financial problems which were serious or persistent or both. Of those previously in paid employment, half had remained in employment for at least 75% of the time between discharge and follow-up interview. Two-fifths of the patients were assessed as likely to benefit from services other than the clinical psychiatric service, which the National Health Service might provide. Skilled home visiting was the primary requirement. A quarter had social needs which might be met from services other than the National Health Service; these needs were most commonly work, social clubs and recreational facilities.

Cancer Mortality in Canada

J. Wyllie (Kingston, Ont.) gave the findings of a study of the comparative mortality index (C.M.I.) as applied to cancer mortality in Canada. It was not expedient to compare the male C.M.I. with the female C.M.I. for the same year; this comparison was made by calculating sex-adjusted ratios. He showed graphs on semi-logarithmic paper of the C.M.I. for cancer by site and sex for the period 1931 to 1957. The base year used was 1944. During this period, for cancer of all sites combined, there was an upward trend in males and a decline in females. Particular attention was drawn to a steady rise in the C.M.I. for cancer of the pancreas, present in both sexes but seen especially in males. Cohort studies on the mortality from cancer at this site were in progress.

The speaker agreed with W. Hobson (W.H.O., Copenhagen) that the interpretation of changes in C.M.I. was difficult but claimed that the use of the C.M.I. was the best method available for indicating trends in mortality. The disadvantage of standardized death rates was that they varied with the choice of the standard population, and equivalent average death rates were unsuitable for the study of mortality at ages over 65.

Immunization Programs in Canada

Canada's experience since 1925 in the prevention of communicable diseases through organized immunization programs was reviewed by R. J. Wilson (Toronto). The recommended schedule was now as follows:

AGE	IMMUNIZING AGENT
3 months	DPT* polio vaccine, 1 ml. (3 doses at 4-week intervals)
Under 1 year	Smallpox vaccine
12-18 months	DPT polio vaccine, 1 ml.
About 3 years	DPT polio vaccine, 1 ml.
About 5 years	DPT polio vaccine, 1 ml.
Under 15 years	Smallpox vaccine
Under 15 years	DT* polio vaccine, 1 ml.
Over 15 years	DT polio vaccine, 0.5 ml.

*DPT is diphtheria toxoid, pertussis vaccine, and tetanus toxoid combined. DT is diphtheria and tetanus toxoids combined.

Applied Epidemiology of Tuberculosis

A. J. Nelson (Vancouver, B.C.) made some observations on the applied epidemiology of pulmonary tuberculosis with special reference to British Columbia. Mortality was no longer a useful measure of prevalence, nor even were first admissions to sanatoria. The reservoir of cases in the community at any time was the important factor. He advocated the study of case-finding indices to ensure the most efficient use of available resources for tuberculosis control. Thus, in evaluating the effectiveness of contact-tracing it was necessary to know the respective numbers of new active cases notified, contacts elicited, new cases found in contacts and, finally, new cases found per 1000 contacts elicited. Contacts elicited per case were classified into household, close non-household, and casual. In mass miniature radiography surveys it was necessary to study the respective numbers of persons screened, new cases and new active cases found, and new cases and new active cases found per 1000 screened. The yield of new active cases from both provincial and metropolitan mobile M.M.R. surveys was falling and the Canadian public health administrator would have to decide when these programs became uneconomic. On the other hand, in a door-to-door survey in which 90% of a community in downtown Vancouver were screened, 50 new cases were detected. If further rapid progress was to be made in the control of tuberculosis more use of the epidemiological method was required.

Canada's National Sickness Survey

G. E. Wride (Ottawa) said that the main objects of the Canadian National Sickness Survey were to obtain estimates of the incidence and prevalence of illness of all kinds; the amount of medical and other health care received; the volume of family expediture for the various types of health services; and the prevalence of permanent physical disabilities. In 1950-51 trained lay enumerators (in one province these were public health nurses) made 14 visits at monthly intervals to a sample of 10,000 households involving 35,000 people. Less than 5% of these households refused to participate in the survey and of the remainder, over 80% of the individuals involved remained in the sample throughout the survey period. For broad categories of illnesses, about 80% agreement

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was obtained between the statements of their illnesses by patients and the diagnoses by their doctors; no estimate was made of illnesses known to the doctors but not mentioned to the enumerators.

A national survey which was not continuing in nature could be regarded as dealing only with a stated period of time which, unfortunately, receded rapidly into history. However, he thought that the current success of Canada's hospital insurance and other social assistance programs was due in large measure to the accuracy of their preparatory estimates which were based substantially on the analyses of the results of the Sickness Survey.

LETTER TO THE EDITOR

THYROID FUNCTION IN APATHETIC HYPERTHYROIDISM

To the Editor:

Drs. Lillington and Brownell's[1] criticism of the article entitled "Thyroid Function in Apathetic Hyperthyroidism" is warranted. Drs. Wilansky, Kalant and Wolfson[2] have divided the two types of hyperthyroidism into the "classical" and "apathetic" types. It is the writer's opinion that the two types of hyperthyroidism are best interpreted by an understanding of the pathological physiology present in each type. The two types of hyperthyroidism can be distinguished by clinical and laboratory examination. An outline of the main distinguishing features and an analysis of the cases presented by Wilansky *et al.* follows:

(A) Hyperthyroidism due to Graves's disease (synonyms are exophthalmic goitre and diffuse hyperplastic goitre).

Clinical Findings:

1. Incidence—the common form of hyperthyroidism.
2. Age—the younger age groups.
3. Onset—usually datable and less than one year before diagnosis.
4. General behaviour—restless.
5. Exophthalmos—present in 40 to 80% of cases in large series.
6. Thyroid storm—may occur.
7. Response to iodine—improvement.

Laboratory Investigation:

1. In the absence of drug therapy the I^{131} uptake is abnormally elevated.
2. Protein bound iodine level is higher than normal.
3. On scintigram examination—there is a diffuse uptake of I^{131} throughout the thyroid gland. This is not altered by thyroid stimulating hormone.
4. Radioautographs of surgically removed specimens from patients who have received tracer doses of I^{131} before surgery reveal a diffuse uptake of I^{131} throughout the thyroid parenchyma. If nodules are present they do not contain I^{131}.

(B) Hyperthroidism due to the autonomous development of hyperfunction in a nodule of a multinodular goitre (synonyms are toxic nodular goitre and Plummer's disease).

Clinical Findings:

1. Incidence—the uncommon form of hyperthyroidism.
2. Age—the older age groups.
3. Onset—insidious, not datable and usually five years or more before diagnosis.
4. General behaviour—quiet.
5. Exophthalmos—not present.
6. Thyroid storm—does not occur.
7. Response to iodine—no improvement—may get worse.

Laboratory Investigation:

1. I^{131} uptake normal in 30% of cases.[3]
2. Protein bound iodine level is very frequently normal.
3. On scintigram examination the I^{131} is localized in the hyperfunctioning nodule. There is no I^{131} in the extranodular tissue. Thyroid stimulating hormone produces I^{131} pickup in the extranodular tissue.
4. Radioautographs from surgically removed specimens in patients who have been given tracer doses of I^{131} before surgery reveal the I^{131} to be localized in the hyperfunctioning nodule with none in the surrounding tissue.

The cases described by Wilansky *et al.* as "classical hyperthyroidism" were subdivided into cases with diffuse goitres and cases with nodular goitres according to the morphological characteristics of the thyroid gland on physical examination. There was no significant difference in the I^{131} uptake or the protein bound iodine in the two subdivisions. They all had a diffuse pickup of radioactive iodine throughout the thyroid gland. The nodules in these goitres do not pick up radioactive iodine and the nodules are a finding unrelated to the hyperthyroidism. On the basis of pathological physiology the cases described as "classical hyperthyroidism" are all examples of Graves's disease.

The cases described by Wilansky *et al.* as "apathetic hyperthyroidism" are examples of hyperthyroidism due to the autonomous development of hyperfunction in a nodule of a multinodular goitre. In these cases the age is significantly older, the I^{131} uptake after 24 hours is significantly lower and the protein bound iodine level is significantly lower. In addition exophthalmos was not present and the I^{131} scintigram revealed localization of the I^{131} within the hyperfunctioning nodule in all cases. They also reported an absence of hyperthyroid signs and symptoms, which is usual in cases of hyperthyroidism due to a hyperfunctioning nodule. On the basis of pathological physiology the cases reported as "apathetic hyperthyroidism" are all examples of hyperthyroidism due to a hyperfunctioning nodule within a multinodular goitre.

A further comment is in order concerning Drs. Kalant and Wilansky's[4] reply to the letter of criticism by Drs. Lillington and Brownell. Dobyns[5] states that if there is hyperthyroidism due to a hyperfunctioning nodule, the remainder of the gland is suppressed in

all cases. He states that exophthalmos is always associated with diffuse hyperactivity throughout the thyroid gland (Graves's disease), and never with a hyperfunctioning nodule in a multinodular goitre. Exophthalmos may be absent in Graves's disease. A multinodular goitre may be present in Graves's disease but it is unrelated to Graves's disease, and the hyperfunctioning thyroid tissue is extranodular.

Drs. Kalant and Wilansky state that hyperthyroidism in cases of "apathetic hyperthyroidism" (a hyperfunctioning nodule) is frequently present with cardiovascular manifestations. This is true. There is no definite evidence that pathological lesions are produced in the heart by the hyperthyroid state.[6] Hyperthyroidism produces cardiac manifestations by increasing the work of the heart. It would therefore accentuate or bring to light underlying heart disease. The incidence of heart disease increases with age. Hyperthyroidism due to hyperfunction of a nodule is a disease of the older groups. Therefore, when hyperthyroidism occurs because of a hyperfunctioning nodule it would be frequently associated with cardiac manifestations.

It is submitted that the two types of hyperthyroidism can be distinguished clinically and on a basis of pathological physiology. Good therapy depends on an exact differentiation between the two types. The concepts of physicians of the early part of this century must be interpreted in the light of present-day knowledge. The terms "apathetic hyperthyroidism" and "masked hyperthyroidism" should be abandoned and the terms hyperthyroidism due to Graves's disease (diffuse thyroid hyperactivity) and hyperthyroidism due to hyperfunction of a nodule in a multinodular goitre should be used because these terms denote pathologic physiological significance to most students of thyroid diseases.

CHARLES H. LOCKWOOD, M.D.

Medical Staff,
Westminster Hospital,
London, Ontario,
August 4, 1959.

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OBITUARIES

DR. WILLIAM W. FRANCIS
1878-1959

AN APPRECIATION

William Willoughby Francis was born in Montreal on April 2, 1878, and died in Ormstown, P.Q., on August 10, 1959. Until he left Montreal for his usual summer vacation, he was to be seen daily in the Osler Library of McGill University, over which he presided with unchanging geniality and zeal for 30 years.

Although born in Montreal, Dr. Francis spent most of his childhood with his five brothers and three sisters in Toronto. Their mother was a first cousin of the celebrated Dr. William Osler, who looked upon the children as his nieces and nephews. He was "Uncle Willie" to all of them, but young Willie Francis was his special favourite.

A graduate of Trinity College School, Port Hope, which always kept its place in his affections, Francis studied both arts and medicine at the Johns Hopkins University, where he obtained the A.B. degree in 1898, the M.D. in 1902. Two years of internship at the Royal Victoria Hospital, Montreal, were followed by another year in Baltimore as a Fellow in Pathology. Then came the *Wanderjahre*. For one, two or three months at a time he studied pædiatrics in London, Berlin, Vienna, Paris, and again London. In November 1906, he commenced practice in Montreal. Concurrently, from 1907 to 1911, he was a demonstrator in pathology at McGill, assisting Dr. Maude Abbott. Soon after his return to Canada he had suffered a pleural effusion and pulmonary tuberculosis forced him, in January 1911, to give up his practice. He remained under treatment at Ste. Agathe for about 18 months. From 1912 to 1915 he was assistant editor of the *Canadian Medical Association Journal* and secretary-treasurer of the Canadian Medical Association. In 1915 he went overseas with No. 3 Canadian General Hospital (McGill) which he served as registrar. Immediately after the war he worked for a time in Geneva, editing all four editions of the *International Journal of Public Health*, published by the League of Red Cross Societies in English, French, Italian and Spanish. From 1922 to 1929 he was occupied, with the help of R. H. Hill, Archibald Malloch and Leonard Mackall, in the compilation of the *Bibliotheca Osleriana*. When the Osler Library at McGill was officially opened on May 29, 1929, Francis was already at work as librarian. For many years he was also lecturer in the history of medicine.

Bill Francis, a master of *æquanimitas*, lived his life contentedly in the shadow of a great man. "In a real sense," wrote E. P. Scarlett in 1956, "he is the extension in time of William Osler—the postcards and notes and letters which were so characteristic of Osler have continued to go forward, carrying the spirit and blessing of W.O. to the far corners of the earth." To create for others a living semblance of Sir William, to catalogue, preserve and augment his library, to cherish his memory in every respect, these were the chief objects of Bill Francis for 37 years. It is therefore, perhaps, too easy to forget that he was an accomplished scholar, superior to Osler in both range and precision. He was an expert bibliophile, but he was more than this, for his knowledge of the older medical literature was extensive and by no means superficial. "His meticulosity exceeds anything you ever met with," wrote Osler. Possibly a tireless concern with minutiæ and an eagle eye for mistakes, linked with incurable facetiousness, concealed from many who knew him a cool, objective mind and uncommon gentle wisdom. He was a remarkable Latinist, seldom at a loss, and could make his way, though with less assurance, in Greek; he was quite at ease in several modern tongues. He picked up languages easily. He was not, however, a trained philologist, and I think it best to describe him as a linguist with the instincts of a scholar. The great *Bibliotheca Osleriana*, with its curious and endear-

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ing combination of careful scholarship and gossipy digressions, is a true picture of its chief editor.

Absolutely without ambition, much given to anagrams, chronograms, crossword puzzles and doggerel verse, a man who preferred Kipling to Tennyson and Tennyson to any modern poet, Francis had a child-like simplicity that never changed or varied. He was willing to devote himself for weeks on end to anyone who needed his help as a bibliographical and historical consultant. His name appears in a thousand prefaces and notes of acknowledgment. It is written large on the hearts of his many friends. They will not soon forget his patience, his gaiety, his wit, his kindness. All of these attributes survived without diminution five episodes of coronary disease; the sixth killed him in the eighty-second year of his youth.

He is mourned by his widow, the former Hilda Colley, by his daughter, Dr. Marian Francis Kelen, and by all who knew and loved him. His ashes will be deposited, with those of Sir William and Lady Osler, in the Osler Library. Canadian medicine, and the international world of medical scholarship, has sustained through his death a substantial loss. When, in 1956, on the occasion of the 35th anniversary of the Osler Society of McGill University, the Society published a volume of 123 pages entitled *W. W. Francis: Tributes From His Friends*, Dr. Thomas J. Sullivan found the perfect quotation in the words of Meredith:

> "That man is good and he alone
> Who serves a greatness not his own
> For neither praise nor pelf:
> Content to know and be unknown
> Whole in himself."

LLOYD G. STEVENSON

WILLIAM W. FRANCIS

AN APPRECIATION

With the death of William W. Francis—"Bill" to his many friends—we have lost, perhaps not the last immediate link with Osler, but certainly one of the most intimate. Indeed, it may be said that it was through him Osler was brought back to us most vividly. His complete devotion to Osler was impressive. Nor was it hero worship in the unthinking sense. There was an added freshness in his transmission of the inexhaustible interest in others and the glancing light-heartedness which yet had always an underlying seriousness of purpose. Osler was at the centre of his thoughts; in latter years it was never long before he managed to turn the talk to him.

And yet Bill Francis was no mere reflective surface of his great kinsman. Deeply as he might submerge himself in the Oslerian tradition he still was a personality. Some idea of the high place he attained in the world of medical literature may be gained from the tributes in the *Festschrift* volume presented to him by his friends a few years ago. This collection will remain as a striking picture of him as projected through many discriminating and affectionate eyes.

He attracted and influenced multitudes of students. If he preached Osler to them it was his own force of character to which they responded, and his own kindliness and wit by which they were attracted. The Osler Undergraduate Society, though actually founded before he came to McGill from the preparation in Oxford of the great *Bibliotheca Osleriana*, owed much to his nourishing interest, serving as one of those few channels through which medical writing derives stimulation and guidance. In discussion of the papers at the Society meetings no inaccuracy escaped his scrutinizing and perceptive attention.

Bill Francis has gone from the wide circle in which he became such a pleasantly familiar figure, ever available and ever reliable. In his chosen field, this is a loss of more than ordinary severity; there are too few in our profession with such mental enrichment as was his. He had an unusual mentor no doubt, but the seed met with the best soil, and from it came the flower of a fine mind, generous and happy-natured, but unyielding in its demand for accuracy, which in the end is truth.

H.E.M.

DR. GEORGE A. W. CURRIE, 45, administrator and superintendent at the Hospital for Sick Children, Toronto, died suddenly from a heart attack while swimming in Lake Ontario on July 15. A native of Picton, Ont., he studied medicine at Queen's University, Kingston, and graduated in 1938. After interning at the Regina General Hospital, Dr. Currie served overseas with the R.C.A.M.C. in World War II and attained the rank of lieutenant-colonel. On his discharge from the Army, he took a postgraduate course in hospital administration. He served as a hospital administrator in Colorado and in Texas before taking up his appointment at the Hospital for Sick Children in 1957.

Dr. Currie is survived by his widow and two sons.

DR. J. KEITH GORDON, 64, medical director of the Sun Life Assurance Company of Canada and past chairman of the board and secretary of the corporation of the Montreal General Hospital, died on August 9 at the Montreal General Hospital. Born in Winnipeg, he studied medicine at McGill University, where he graduated in 1920. He did postgraduate work at Harvard Medical School and in Montreal. A veteran of two world wars, Dr. Gordon served overseas with the 7th Siege Battery, Canadian Garrison Artillery in the First World War, and in World War II, as a Lieutenant-Colonel, he was officer in charge of the Medical Division No. 1, Canadian General Hospital, Overseas Service. In 1924 Dr. Gordon joined the Sun Life Assurance Company as assistant medical officer and in 1946 he was appointed medical officer. Five years later he became medical director and an executive of the Company. For many years Dr. Gordon was connected with the Montreal General Hospital, of which he was a governor and a member of the consulting staff. He was also a former professor of medicine and clinical medicine at McGill.

Dr. Gordon is survived by his widow and two daughters. A son, Peter, was killed overseas during World War II while serving with the R.C.A.F.

DR. DENNIS JORDAN, 75, died of a heart attack at his Toronto home on July 7. A graduate in medicine from Queen's University, Kingston, in 1910, he did postgraduate work in England, Ireland, Austria and Germany. Dr. Jordan practised in Toronto for over 45 years before his retirement last year.

He is survived by his widow, two sons and a daughter.

PUBLIC HEALTH

THE 12TH WORLD HEALTH ASSEMBLY

The World Health Assembly, policy-making body of the World Health Organization, held its twelfth meeting in Geneva from May 12 to 29, 1959. The sessions were formally opened by the President of the Assembly for 1958-59, Dr. Leroy Burney, Surgeon General of the U.S. Public Health Service, elected to this office at the session in Minneapolis, Minnesota, last May.

After the examination of credentials of all delegates, the first formal action of the Assembly was to appoint its President for the forthcoming year and by unanimous vote Sir John Charles, Chief Medical Officer, Ministry of Health for the United Kingdom, was elected. As Vice-Presidents, Dr. M. B. El-Azmeh, United Arab Republic, Dr. V. Marinesco, Rumania, and Dr. O. Souvannavong, Laos, were also unanimously elected. To preside over the two main committees of the Assembly, Program and Budget, and Administration, Finance and Legal Matters, Dr. H. B. Turbott of New Zealand and Dr. O. Vargas-Mendez of Costa Rica were also unanimously chosen.

In addition to electing the presiding officers, the chief functions of the Assembly in plenary session, in deciding on a program and budget for the forthcoming year, are the allocation of agenda items to the two main committees, consideration of the report of the Director-General on the work of the organization over the previous year, dealing with the admission of new members, electing those members entitled to designate a person to serve on the Executive Board of W.H.O., presentation of any awards or prizes under the auspices of the organization, and dealing with the reports of the day to day work of the main committees.

The admission of Guinea as an independent state was acclaimed in an early plenary session and during the course of the Assembly it was announced that as of May 14, 1959, Colombia had formally ratified the Constitution of W.H.O. and, therefore, became entitled to full membership. With these two additional states, the total membership of the organization numbers 87 of which 84 are full members and three associates.

In the matter of election of members entitled to designate a person to serve on the Executive Board, with the retirement of Canada, Mexico, United Kingdom, Italy, Tunisia and India, after the regular three-year term, the following Member States were named to make up the full membership of 18 independent experts serving on the Board: Peru, Venezuela, Ireland, Luxembourg, Sudan and Nepal.

In the Program and Budget Committee the regular program and budget for 1960 recommended by the Director-General was approved after close scrutiny of its content. The total amount involved approximated $16,400,000.

However, an additional proposal was made to add $500,000 to the regular budget for an intensified program of medical research for W.H.O. arising out of a study of the role of the organization in medical research initiated by a contribution of $300,000 by the U.S. Government at the 11th World Health Assembly. This resulted in a total effective working budget of $16,918,700, an increase of some $1,970,000 over that for 1959 which, with supplementary estimates for unanticipated statutory requirements and an initial credit to the Headquarters Building Fund, had itself been increased by $662,000 over the amount approved at the 11th World Health Assembly. Thus the net increase for 1960, including the provision for medical research, approximated 13%.

The report of the study of the role of W.H.O. in medical research was submitted to the Committee in a comprehensive document. It indicated that some $2,200,000 might be expended in the initial year of an expanded research program, but in the face of determined opposition because of the precipitate manner in which the report had been introduced and the magnitude of the initial effort, a working party was established and, after further study, recommended that an amount of $500,000 be provided. This was approved by majority vote.

A related item dealt with the consideration of an International Health and Medical Research Year arising out of a resolution of the General Assembly of the United Nations and a proposal by the U.S. Government. This met with even greater opposition because of the vagueness of the definition and content of the "year", especially in the light of its being implemented, as suggested, in 1961. While it was more or less indefinitely postponed after prolonged discussion in the Committee, when dealt with in plenary session it was decided to reconsider the matter at the 13th World Health Assembly, the Director-General and Executive Board being requested to study it further and report to the next Assembly.

In the Committee on Administration, Finance and Legal Matters a number of equally important items were considered. In addition to the review of the adequacy of the Program and Budget Estimates for 1960, the Committee dealt with two proposed constitutional amendments, the problem of headquarters accommodation for the Secretariat, an agreement between W.H.O. and the International Atomic Energy Agency, a request by the U.S.S.R. to participate in the work of the Regional Committee for South East Asia, the status of the Malaria Eradication Special Account and the continuation of the Director-General's term of office for an additional three years.

One constitutional amendment which was proposed by the United Kingdom was to increase the size of the Executive Board from 18 to 24 members. This ultimately received the two-thirds majority vote required for a change in the Constitution, and when ratified by two-thirds of the Member States, the increase will come into effect.

The other amendment had to do with a change in the periodicity of World Health Assemblies from annual to biennial frequency. Having been considered on several previous occasions, its inclusion on the agenda for this meeting was a Canadian initiative and the matter was discussed in detail. While supported generally by the Member States with more highly developed health services because of the savings in funds, time of health workers at all levels and other advantageous features, the proposed change was strongly resisted by others, mainly the relatively underdeveloped countries. As a result, the amendment failed to obtain the necessary two-thirds majority and further consideration of any such modification was postponed in the belief that it would not be opportune at a time when the organization is expanding and its activities developing to reduce the number of occasions upon which the Assembly should meet.

The inadequacy of facilities for the Secretariat in the Palais des Nations in Geneva having become increasingly apparent, the matter of headquarters accommodation has been studied over the past several years. After consideration of this study the Assembly approved the initiation of action towards the construction of a Headquarters Building to be located adjacent to the Palais and to utilize its existing conference facilities. It is estimated that this will extend over some four years in planning and construction, at a cost approximating $10 million. In financing this project, the Swiss Government and the Government of the Canton of Geneva have offered most generous loans, the former, the equivalent of $5 million on an interest free basis, and the latter, half this amount at a low rate of interest. The organization expects to obtain some reimbursement for expenditures already made in expanding office facilities in the Palais so that the greater part of the funds estimated for the new building will be currently available. A worldwide but selective competition will be held with respect to the architectural design of the new building.

Less encouraging is the matter of the Malaria Eradication Special Account, the special fund established for a concerted drive over a period of 5 to 8 years, or longer if necessary, to eradicate malaria throughout the world. Sufficient funds are available to complete planned activities for 1959 and it is understood that the U.S.A. will contribute

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$3 million for the 1960 program. The estimated total required for 1960 is in excess of $7 million and Member States have been urged to contribute generously on a voluntary basis to achieve this goal.

A formal agreement between the World Health Organization and the International Atomic Energy Agency respecting the rights of both bodies in the matter of health aspects of atomic energy and radioactive materials, already approved by the Governing Council of I.A.E.A., was given unanimous approval by the 12th World Health Assembly.

A request by the Soviet Government to participate in the work of the Regional Committee for South-East Asia was rejected by the Committee on Administration, Finance and Legal Matters. With its seat of government in the European Region, the Soviet Union, as well as the Ukrainian S.S.R. and Byelorussian S.S.R., the latter two presently inactive, are Members of the Regional Committee for Europe. However, arguing that the contiguity of some of its Member Soviet Republics in Asia and the similarity of disease problems between these states and adjacent countries in South-East Asia, e.g. Afghanistan, justify participation in the Regional Committee in that area, the Soviet delegation pressed for approval of its request. This was opposed on constitutional grounds by a number of members. The original Soviet request was withdrawn when a compromise resolution was submitted by the Polish delegation requesting further study and definition of regional boundaries by the Executive Board. This, however, was defeated when put to a vote.

An item which stimulated keen interest was initiated by the New Zealand delegate and related to the continuation of the appointment of the Director-General, Dr. M. G. Candau, for an additional period of three years, i.e. to complete his second five-year term of office. The draft resolution was co-sponsored by 33 Member States, with an additional three asking to be included, and the proposal was commended by some 20 delegates during a closed session of the Committee. It was approved unanimously and the Director-General, in expressing his appreciation for this indication of confidence in his leadership, assured the Assembly that he would make public his decision at the earliest reasonable opportunity.

In concluding its business, it was decided that the 13th World Health Assembly will meet in Geneva in 1960.

The Canadian Delegation to the 12th World Health Assembly was led by Dr. G. D. W. Cameron, Deputy Minister of National Health, with Mr. Max Wershof, Ambassador and Canadian Permanent Representative to the United Nations in Geneva, as alternate head, and Dr. J. E. Bissonnette, M.P. for Quebec West, the third delegate in the role of parliamentary observer. Alternate delegates were Dr. G. F. Amyot, Deputy Minister of Health for the Province of British Columbia, and Dr. B. D. B. Layton, Principal Medical Officer, International Health Section, Department of National Health and Welfare, with Mr. R. Harry Jay, First Secretary, Permanent Mission, Geneva, Adviser.

Dr. Amyot was appointed a group discussion leader for the technical discussions on health education, under the overall guidance of Sir Arcot Mudaliar of India. Canada was elected to the General Committee, which under the chairmanship of the Assembly President, acts as the "steering" committee for the business of the Assembly. The Canadian delegation also participated in the work of the sub-committee on Legal Matters of the Committee on Administration, Finance and Legal Matters, and Environmental Sanitation of the Committee on Program and Budget.

Dr. Percy E. Moore, Director of Indian and Northern Health Services, Department of National Health and Welfare, and Chairman of the Executive Board of W.H.O. for 1958-59, was the designated representative for the Board at the Assembly.

B. D. B. LAYTON

PROVINCIAL NEWS

BRITISH COLUMBIA

In a report for the past year from the Workmen's Compensation Board, we note that the forest industries of British Columbia have the lowest rate of accidents in their history—44.44 per million man-hours worked. Ten years ago the rate was 102.37 and it has declined steadily since then.

The low accident rate is especially seen in sawmills, where of seven large companies, four had a record of no accidents at all, and the other three had extremely low rates. Logging, for so long one of the most hazardous occupations in industry, still has a fairly high rate—46 per million in five large operations, of which two had no accidents at all, these being small with less than 150,000 man-hours between the two.

A great deal of this improvement was due to education and publicity, and an excellent system of first-aid.

The Quarantine Station, which for so many years was located at William Head, has been moved downtown; future inspections of ships, when necessary, will be done from craft supplied by the British Columbia Pilotage Authority.

Dr. S. F. Blundell is the medical officer in charge, replacing Dr. B. Jenkins, who retired recently after many years of service.

The enquiry into British Columbia's mental health needs and resources began in August. This enquiry was promised early this year, to clear up the whole question of mental hospital care, following the controversy aroused by the action of the government last year in curtailing these activities.

The American Psychiatric Association was asked by the British Columbia Government to conduct this enquiry, and Dr. Mathew Ross, medical director of the American Psychiatric Association, is in charge. He is being assisted by a team composed of members of the Canadian Mental Health Association and its B.C. Division, the Canadian Medical and Psychiatric Associations, the Department of National Health and Welfare, the Provincial Department of Mental Health Services, the Department of Psychiatry of the University of British Columbia, and more than 20 expert consultants from Canadian and American universities.

Seven public meetings were held across the province in August in Victoria, Vancouver, Nanaimo, Nelson, Kelowna, Kamloops and Prince George.

Hospital accommodation in Vancouver is becoming critical, and the press is beginning to comment on it. Doctors, of course, have known this for a long time.

A survey made by a local newspaper finds that the available beds in the city are below the minimum U.S. standard of 4.4 beds per 1000 people; that cases of cancer, heart disease, etc., have often to wait for months before a bed can be obtained; that a waiting list of from 2000 to 3000 people exists, and so on; that too many beds are occupied by chronically ill patients for whom accommodation elsewhere cannot be found.

In Vancouver, of course, there are certain special factors; 25% of patients come from outside Vancouver —this for many reasons.

One cause, the absence of chronic hospitals is probably the greatest evil. Patients have to be kept in acute beds too long; many "chronics" stay for months in acute beds needed for conditions urgently requiring hospitalization. Promises of chronic hospitals bubble forth periodically from provincial and municipal sources, but nothing is done. New "acute" beds are slow in coming—and hospitals take time to build.

No doubt, other large centres in Canada have similar tales to tell. But the Vancouver press and public are beginning to realize the seriousness of the situation.

At the time of writing, the press is hot on the trail of "chronic" hospitals. Premier Bennett, in a speech made at Kelowna recently, stated that the province will now have money to spend on chronic hospitals. Vancouver is pressing hard for these. One practical and constructive offer has come from the Roman Catholic Church in Vancouver, which has stated through Archbishop Martin Johnson that the Catholic Church is prepared to build a 200-bed chronic hospital if the civic, provincial and federal governments are willing to assist in the cost of construction. The Church will be responsible for operating costs and staffing—will accept the rates paid by the provincial government for care of patients in private hospitals. The chronic hospital would be for permanent and incurable disabilities. J. H. MACDERMOT

MANITOBA

Dr. F. R. Tucker has been named chief of orthopædics in the department of surgery, University of Manitoba, with the rank of assistant professor. He succeeds Dr. George Ryan, associate professor, who has held the post since 1947.

Dr. M. E. Bristowe, assistant superintendent of the Brandon Mental Hospital, has been named hospital superintendent, succeeding Dr. Stuart Schultz, who is retiring. Dr. Bristowe (M.D. Manitoba 1930) served at the Portage Hospital for Mental Defectives before going to Brandon.

The new Riverdale hospital at Rivers will contain 20 beds, 10 bassinets and 9 nurses' beds. The Department of National Health and Welfare will contribute $74,416 to the cost of construction.

Construction of a fully modern physiotherapy and occupational therapy unit at Assiniboine Hospital, Brandon, will start this fall. A one-storey fireproof building measuring 4800 square feet, it will be joined to the present hospital and will provide facilities for hydrotherapy, wax baths and electrotherapy and equipment for exercising and strengthening muscles.

A former patient at Assiniboine Hospital has recently been appointed manager of a jewellery store in Fort St. John, B.C. He is the only fully qualified Indian watchmaker in Canada. Another ex-patient who took advantage of the rehabilitation service of the Manitoba Sanatorium Board is one of the few Eskimo watchmakers in Canada.

Clearwater Lake Hospital was a busy place recently when 13 Eskimo and Northern Indian patients were being discharged. They were taken by R.C.M.P. plane to a community centre at Fort Churchill and thence to their respective homes. They will be replaced by other patients. Ten of the discharged patients were Eskimos.

Manitoba Health Service, the prepaid medical plan formerly known as Manitoba Medical Service, proposes to restrict service coverage to subscribers below a certain income level. This level has not yet been determined. Those with incomes above this level will not be able to purchase from Manitoba Health Service indemnity against the costs of illness. Experience has shown that people in the higher income brackets demand a higher standard of medical care and make more use of the medical service provided.

The Manitoba legislature has given approval in principle to a bill giving the Manitoba Hospital Service Association (Blue Cross) permission to use its surplus funds of about one million dollars to build a radiation treatment and research foundation. The Hon. George Johnson, Minister of Health, says that present facilities for treatment and research in cancer are becoming inadequate.

Sixty-five members of the Manitoba Division, Canadian Medical Association, left Winnipeg by chartered plane for Edinburgh to attend the joint meeting of the British and Canadian Medical Associations, July 16 to 24.

Hospital Insurance Plan premiums will not rise in the coming year. Total cost of the plan in Manitoba is $27 million of which $11 million comes from the federal government, $13 million from premiums and $3 million from the provincial government.

Dr. Kenneth C. McGibbon of Winnipeg has been invested at a private ceremony in London as a Knight of Grace, Venerable Order of the Hospital of St. John of Jerusalem, by Baron Wakehurst, lord prior of the order and governor of Northern Ireland. Dr. McGibbon, an orthopædic surgeon, has been connected with the order since 1935 and from 1944 to 1956 he was provincial commissioner.

A bill which would allow chiropodists to have extended powers of treatment was thrown out in the Manitoba legislature law amendments committee.

ROSS MITCHELL

QUEBEC

The highlight on activities in our area in July was the ninth International Congress of Pædiatrics which was held during the week beginning July 20, at the Queen Elizabeth Hotel in Montreal. Some 3000 delegates from 85 countries were in attendance under the presidency of Dr. Alan Ross, the physician-in-chief of the Montreal Children's Hospital. It was an exciting week of scientific reports and discussions on problems ranging from basic research to the practical common sense problems encountered by pædiatricians everywhere and everyday. According to comments heard from many of the delegates, it was a first-class success

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scientifically as well as socially. The greatest success probably has been for its bringing together, for the benefit of the world's children and mankind, of knowledge gathered in many medical and scientific fields. Reports by biochemists and biologists dealt with various fundamental processes of human life and reproduction. The geneticists extended this so that their contributions may open enormous possibilities of control in genetic heritage. Many reports dealt with the problems of cancer in children. The prevention of accidents, now listed the chief killer of children all over the world, was given prominent emphasis.

The scientific program of the Congress was under the direction of eight chairmen: Dr. Louis Diamond, Boston; Dr. Richard Masland, Bethesda, Md.; Dr. Bruce Chown, Winnipeg; Dr. Joseph Stokes, Jr., Philadelphia; Dr. Clement A. Smith, Boston; Dr. E. Emmett Holt, Jr., New York; Dr. L. K. Pickett, Syracuse, N.Y.; and Dr. Charles Janeway, Boston. These chairmen did an excellent job in summing up the activities of the 82 separate and often concurrent sessions held during the week.

The next congress, the tenth, will be held in 1962 in Portugal and the incoming president for this congress will be Professor Salizar de Sousa. He presented Portugal's invitation, having been selected to do so by the Pædiatric Society of Portugal.

Mr. F. B. Common, Jr., president of the Verdun Protestant Hospital, has announced the receipt of a grant of $2,225,000 for construction and alterations at the hospital. This has been granted by the Quebec government to finance the long-needed program of renovation and construction at the 69-year-old mental hospital, which serves the English-speaking community in the province. The renovations will include all the six patient buildings, while the new construction will include the new 150-bed medical-surgical building, a 100-bed continuous-care building and a 25-bed addition to the nurses' residence. Work on these projects will begin immediately.

The total cost will be about $4,000,000 of which $2,225,000 is covered by the provincial grant. The rest will come from the federal government through the province as a federal-provincial health grant, with $750,000 to be financed by the hospital.

Members of the special committee for the Research Fund in memory of Dr. William Cone of the Montreal Neurological Institute have now been named. These are Judge Thomas Tremblay, Samuel Bronfman, Arthur Jensen, T. R. McLagan, C. W. Webster, Edward C. Wood and Dr. Wilder Penfield, co-founder of the Institute. The Cone Research Fund, set up in May of this year, has now reached a total of $200,000, and the new committee hopes to build this up through public support to a very substantial endowment.

Annual bursaries have been granted to three Montreal physicians by the Canadian Cancer Society. This will allow them to continue studies of cancer treatment and detection in the United States. Dr. Robert Blackburn, a graduate of Laval University and on the staff at Notre-Dame Hospital, will train in therapeutic radiology at Harper Hospital in Detroit. Dr. Gérard Ostiguy, also on staff at Notre-Dame Hospital and a graduate of the University of Montreal, will study cell cytology at the Jackson Memorial Hospital in Miami, Fla. Dr. Michel Lacombe, on the staff at Maisonneuve Hospital, will engage in further study and research at the Graduate Hospital in Philadelphia. These grants have all been made available through the John S. McEachern Memorial Fellowship Fund.

On July 29, Dr. Harold R. Griffith, medical superintendent of the Queen Elizabeth Hospital in Montreal and former chairman of the department of anæsthesia at McGill, received special honours from the Royal College of Surgeons in London, England. At a special session, he became the first Canadian to be presented with an honorary fellowship in the Faculty of Anæsthetists, and one of four persons ever to be so honoured. Dr. Griffith has been associated with the Queen Elizabeth Hospital for 43 years, more than half of it as medical superintendent. He is the son of the late Dr. A. R. Griffith, one of the founders of the same hospital in 1894, then named Homœopathic Hospital of Montreal. We wish to join his many friends and associates in congratulating Dr. Griffith for achieving this high honour.

Dr. Arthur Vineberg, surgeon-in-chief of the subdepartment of cardiac surgery at the Royal Victoria Hospital, is the only Canadian among a group of 34 specialists taking part in an international symposium on heart and blood vessel diseases now taking place in Bogota, Colombia. The conference is the first of its kind and is sponsored by the Shaio Foundation of Bogota.

A. H. NEUFELD

ABSTRACTS *from current literature*

MEDICINE

Honeycomb Lungs and Malignant Pulmonary Adenomatosis in Scleroderma.

H. CAPLAN: *Thorax*, 14: 89, 1959.

Two case reports of scleroderma include findings at necropsy. The first was in a woman aged 42, who had scleroderma for about 16 years. At death the disease was very widespread, affecting fingers, limbs and the œsophagus. The heart showed hypertrophy of the myocardium, dilatation of the left ventricle, and considerable atheroma of the coronary arteries and the aorta. A system of thin-walled cysts about 1-2 mm. in diameter was found in sections of the lower lobe of the right lung. These cysts were filled with mucopurulent exudate and were lined by epithelium which at times merged with tubular masses of polygonal cells apparently invading fibrous lung stroma. In the left lower lobe, congestion, chronic bronchitis, slight emphysema and fibrosis were found. In the second patient, a woman aged 60 years, there was a long history of "arthritis". The scleroderma involved her face and hands and there was also massive left pleural effusion. On aspiration, the pleural fluid was found to be heavily bloodstained and to contain malignant cells. The patient died soon after admission, and at autopsy the left lower lobe was found to be collapsed, while the base of the right lung showed an area of spongy fibrosis. Here also cysts and tubules of varying

shapes and sizes were seen in sections of the base of the right lung, and squamous metaplasia was present. In the left lower lobe, similar formations were adjacent to and blended with an area of tubular, trabecular, cuboidal and polygonal-celled carcinoma.

Discussing these findings, the author states that whilst the impression in the first case was of neoplasia, there was no unequivocal evidence of invasion or of metastasis. The case is considered one of pulmonary adenomatosis with pre-malignant (possibly early malignant) changes. In the second case the carcinomatous nature of the disease is beyond doubt. The relationship between pulmonary adenomatosis and chronic lung damage due to various agents producing interstitial inflammation and fibrosis is discussed and the relationship between pulmonary fibrosis and scleroderma is pointed out. Shortness of breath in cases of scleroderma is not necessarily due to stiffness of the chest wall but may be the result of fibrosis or cystic changes in the lung.

W. GROBIN

Intestinal Angina.

W. P. MIKKELSEN AND J. A. ZARO, JR.: *New England J. Med.*, 260: 912, 1959.

Intestinal angina due to circulatory insufficiency of the abdominal aorta or its gastro-intestinal branches may exist for weeks, months or years before complete occlusion of the mesenteric artery occurs. The syndrome consists of postcibal distress such as cramping abdominal pain with radiation to the back. It develops 15-30 minutes after eating and may last 1-3 hours. The case of a 62-year-old man is reported who had suffered from abdominal pain intermittently after meals for two years. The pain was of a squeezing, bloating character and centred in the upper and right portions of the abdomen. A heavy meal was especially likely to precipitate it, and occasionally it was associated with and relieved by vomiting. Claudication of the left hip, thigh and calf developed after the patient walked two blocks and was relieved by rest. Chronic pancreatitis was suspected but could not be confirmed. Anticholinergic medication seemed to afford some relief, and the patient gained some 5 lb. of the 40 lb. which he had lost since the onset of the distress.

On his second hospital admission he had lost some weight and there was a steady increase in the frequency and severity of the pain. On this admission aortic pulsations were palpable up to 2.5 cm. above the umbilicus, and the iliac, femoral, popliteal and pedal pulsations were absent bilaterally. There was an increase in abdominal-wall arterial collateral circulation. At laparotomy the inferior mesenteric artery was occluded and the superior mesenteric artery with its intestinal branches were pulseless. The aortic occlusion started just below the renal arteries and extended to the external iliac arteries bilaterally. Periaortic cicatrization narrowing the first few centimetres of the superior mesenteric artery was the principal cause of obstruction, although ostial atherosclerosis existed as well. The encircling tissue was excised and endarterectomy was carried out with the use of a wire-loop instrument designed by Cannon and Barker. After closure of the arteriotomy, visible pulsations returned to the artery as well as to its smaller branches. Anticoagulant therapy was started a few days afterwards and is being maintained. During the two months since the operation there has been a gain in weight of 3.6 kg., the syndrome of intestinal angina has completely disappeared, and constipation, which had been a very severe problem before, is now of no consequence.

The authors state that they have identified six cases of intestinal angina during the last two years but only the case reported in this paper was recognized before the onset of intestinal gangrene. They believe that this is the first case recorded in which the diagnosis was recognized preoperatively and in which successful treatment was carried out before more acute symptoms developed.

W. GROBIN

Tuberculoma of the Brain with Tuberculous Adenitis and Epididymitis.

S. R. COGAN AND J. S. BORNSTEIN: *Ann. Int. Med.*, 50: 796, 1959.

The incidence of intracranial tuberculoma has decreased markedly over the last half-century, paralleling the decrease in tuberculosis in general. This is related to better living standards, effective antimicrobial agents, intensive case-finding surveys, and a better understanding of the pathogenesis of the disease. The pathogenesis of intracranial tuberculoma is believed to depend on hæmatogenous spread of the bacilli, either at the time of the primary complex or at a later time, due to reactivation of a previously quiescent lesion. Activity of the lesion in the central nervous system, as in lesions at other sites, depends upon a number of factors. The usual presenting symptoms of a clinically significant intracranial tuberculoma are those of an expanding intracranial lesion, with or without focal neurological signs.

Before the advent of streptomycin, the postoperative incidence of meningitis was practically 100%, and it was uniformly fatal. This has dropped to an incidence

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of from 10 to 20% with streptomycin, and the outlook for the future is even better with more recently developed antimicrobial agents, especially isoniazid. It is considered that tuberculous meningitis usually results from contamination of the meninges by breakdown of a continuous lesion within the brain which was present before the development of the meningitis. The preoperative diagnosis of intracranial tuberculoma in patients with expanding intracranial lesions may be made if there is evidence of additional extrapulmonary tuberculosis. This is of importance in the early institution of antimicrobial therapy. Patients with intracranial tuberculoma should be periodically checked for development of other extrapulmonary lesions. To prevent the postoperative meningitis as well as to treat occult sites of tuberculosis, long-term antimicrobial therapy for at least two and probably three years should be carried out in these patients after operation.

A case, diagnosed preoperatively, of intracranial tuberculoma with tuberculous adenitis and epididymitis is presented. S. J. SHANE

Coronary Embolus with Myocardial Infarction and Rupture.

A. P. GELPI AND N. ENDE: *Ann. Int. Med.*, 50: 511, 1959.

An unusual case of coronary embolism occurred after colectomy for intractable ulcerative colitis. A 66-year-old man had had diarrhœa and melæna for five months and had not responded to adrenal steroids or amœbicidal therapy. The illness was complicated by the development of thrombophlebitis of the right leg and pulmonary infarction. Sigmoidoscopy and roentgenography revealed typical findings of ulcerative colitis. The findings disappeared when the colon was resected. The postoperative course was complicated by a wound infection caused by *Staphylococcus aureus*, which proved resistant to most of the available antibiotics. The patient died suddenly.

Necropsy showed that the immediate cause of death was a myocardial rupture following an infarction. The anterior descending branch of the left coronary artery had been occluded by a septic embolus, originating in a fresh vegetation on the dextro-posterior aortic cusp. In all, two lung abscesses were demonstrated. From these, hæmolytic *Staphylococcus aureus* was cultured, of a behaviour and antibiotic resistance identical with those of the organisms isolated from the wound infection. The coronary embolus consisted of masses of coccoid organisms.

A review of the literature confirms the rarity of coronary embolism. In previously reported cases, death occurred before myocardial infarction could develop to so massive a degree. The authors believe that this is the first published example of myocardial rupture caused by septic coronary embolism. S. J. SHANE

SURGERY

Some Nontechnical Aspects of Open Heart Surgery in the Community Hospital.

A. R. HENDERSON *et al.*: *J. A. M. A.*, 170: 28, 1959.

Open heart operations are feasible within hospitals outside the big centres. This article describes the problems of organizing such service under the headings of availability of case material, the assembling of a team, preliminary experimental experience, preoperative evaluation and selection of patients, and the difficulties at the beginning. The message which the authors wish to impart is as follows: "Given a trained surgeon and an interested and dedicated group of workers in a community hospital, there may be excuses but there are no real reasons why this newest surgical innovation can not be added to the protocol. Postponement, the putting-off that usually waits for supposedly better times, circumstances, conditions, or machines, may cost a hospital an opportunity to take a giant scientific step forward. Patients, too, will be denied their rightful opportunity for this recent and effective treatment." W. GROBIN

Hypothermic Analgesia for Open Heart Surgery with the Heart-Lung Machine.

W. W. MUSICANT *et al.*: *J. Thoracic Surg.*, 37: 184, 1959.

A new concept of hypothermic analgesia for extracorporeal open heart surgery is presented. Except for a muscle relaxant, no other anæsthetic adjunct was required to maintain surgical anæsthesia during bypass.

Fifteen patients underwent surgical correction of their cardiac defects using this technique and all reacted identically, with one exception. This patient had a prolonged succinylcholine effect. He was awake at the end of the operation but required assistance to respirations for about 30 minutes postoperatively. Although preoperative drying agents were not used, respiratory secretions were not a problem. The usual cardiac slowing, seen under hypothermia, was not encountered in any of the cases.

The types of operation and the ages of the patients are described. With one exception, all patients did extremely well postoperatively. This patient died 18 hours after operation. Although attempts were made to prevent cardiac tamponade, a thick clot formed around the heart and produced tamponade. The patient was alert until shortly before death. Necropsy revealed the tamponade and excellent closure of the interatrial and interventricular septal defects. In subsequent operations the pericardial sac has not been closed.

The length of time of bypass varied from 16 minutes to 42 minutes. Careful questioning revealed that no one had any recollection of any part of the operation. All patients remembered going to sleep, and the younger patients remembered only the stories they were told during the induction. S. J. SHANE

Transparietal Splenoportography in Diagnosis of Epigastric Tumours *(in Russian)*.

I. RESH, I. BRET AND M. LISKOVA: *Khirurgiya*, No. 2: 20, 1959.

The technique of, indications for and value of splenoportography are discussed. The changes in the splenoportogram are outlined in the various intra-abdominal diseases. In 61 cases of gastric neoplasm, this investigation was of limited value. Although it frequently outlined displacement of the spleno-portal vessels, it did not contribute any specific information except in six cases where metastases invaded the lumen of the veins. Of 12 cases of tumours of the colon eight were associated with a normal splenoportogram, but in two metastases of the liver were indicated. In two patients unexpected complete obstruction of the portal artery was discovered. In 21 patients with tumours of the pancreas the value of this method of investigation was shown most clearly. Marked involve-

ment, displacement and obstruction of the vessels were found in 11 cases, in which no other evidence calling for abdominal exploration was obtained. In retroperitoneal tumours which were either primary or secondary, splenoportographic findings were markedly abnormal in five cases, confirmed a clinical impression in four others, and showed no abnormalities in three. It was possible to distinguish between expanding and infiltrating tumours. In 44 patients with malignant, mostly metastatic tumours of the liver, this diagnostic procedure was extremely useful and at times the only method available to diagnose the disease. W. GROBIN

Patterns and Dynamics of Tracheobronchial Deformity in Pulmonary Tuberculosis.

G. A. P. HURLEY AND D. TODOSIJCZUK: *J. Thoracic Surg.*, 37: 166, 1959.

Evidence is presented of the undesirable effects of upward displacement of the hilus, particularly on the left side, in chronic pulmonary tuberculosis. This points up the need for vigilance, especially in tuberculosis of the left upper lobe, to anticipate and if possible prevent the destructive effects of this displacement. Prevention is best served by prompt treatment of the tuberculosis in order to diminish the amount of contracting scar tissue. The writers suspect also that the reduction or elimination of useless forcible cough is important.

In order to interrupt the deforming process, they advise surgical removal of the contracting mass of fibrous tissue in the left upper lung as soon as it is observed to be causing abnormal curvature of the left main-stem bronchus, and abnormal angulation at the junction of the left main stem and left lower lobe bronchi. This would, of course, be a new indication for removing an area of disease, even though apparently healed, in the left upper lung. In cases in which, for some reason, resection of the left upper lung is not practical, an alternative might be found in upper thoracoplasty with apicolysis, pushing the contracting mass down to the level of the hilus where its upward pull is neutralized.

When deformity is already far advanced and the left lung syndrome well established, there is less hope for useful remedial measures. However, resection of the left upper lobe with upper thoracoplasty does seem to correct, at least in part, the abnormal curvatures and angulation, and in this way tends to interrupt the harmful series of events leading to loss of function of the left lower lobe. S. J. SHANE

PÆDIATRICS

Follow-up of Children with Tuberculous Meningitis with Special Reference to Psychiatric and Neurological Aspects.

J. LORBER: *Proc. Roy. Soc. Med.*, 52: 269, 1959.

One hundred consecutive surviving children who had been treated for tuberculous meningitis and who had been observed for 3-10 years were frequently rechecked by intelligence tests, repeated electroencephalography, and audiometry. The vast majority were only slightly retarded or had a normal I.Q. The severely retarded children were all two years of age or younger at the time of their illness; 12 of the children had considerable neurological residual lesions and 35 were reported as being dull at school. Two had major personality disorders and three girls showed precocious sexual behaviour. Forty-five children developed intracranial calcifications and in 41 the EEG failed to return to normal. W. GROBIN

OBSTETRICS AND GYNÆCOLOGY

Virus Diseases in Pregnancy and their Effects on the Fetus.

M. GREENBERG: *Am. J. Obst. & Gynec.*, 77: 620, 1959.

The plan of study and preliminary results of a prospective study on virus diseases in pregnancy under controlled conditions in New York City are described. The immediate, direct relationships observed in the first 89 cases reported in the study were fetal death, neonatal infection and maternal death. Other effects, like prematurity and malformation, were randomly distributed between viral and control groups.

The occurrence of congenital heart disease and mongolism in the control group only emphasizes the need for controlled studies in evaluating results associated with German measles. ROSS MITCHELL

DERMATOLOGY

Anaphylactic Shock after Therapy with Penicillinase.

A. L. HYMAN: *J. A. M. A.*, 169: 593, 1959.

The author reports a case where two minutes after an intramuscular injection of 800,000 units of penicillinase the patient complained of weakness, dizziness and dimness of vision. Orthopnœa, wheezing respiration and cyanosis developed. The blood pressure and pulse were not obtainable and the heart sounds were irregular and about 30-40 beats per minute. Intravenous adrenaline and systemic steroids were given, and the patient recovered. The author points out that penicillinase is a bacterial protein enzyme and as such has its own allergic properties. ROBERT JACKSON

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THERAPEUTICS

Treatment of the Hamman-Rich Syndrome with Cortisone.
J. READ AND R. A. B. HOLLAND: *Thorax*, 14: 71, 1959.

A case of acute diffuse interstitial pulmonary fibrosis in an Italian woman aged 39 years is reported. Dyspnœa of effort developed very shortly after a course of intramuscular injections of penicillin and 14 days of sulfonamide therapy for a breast abscess. Her dyspnœa worsened when she was given, one month later, another four weeks' therapy with a sulfonamide. Four months after the first course of penicillin and sulfonamide she was investigated at a thoracic unit in hospital. A chest radiograph at that time showed a fine generalized reticular mottling over both lung fields. She had clubbing of her fingers and mild cyanosis of lips and fingers, and her respiratory rate was increased to 30-40 per minute.

The differential diagnosis included sarcoidosis, eosinophilic granuloma, carcinomatosis and pulmonary adenomatosis. The two latter possibilities as well as pneumonoconioses or other fibrosis were excluded by the subsequent course of the disease. The history and the severity of respiratory disability were in favour of acute diffuse interstitial fibrosis. The patient was given cortisone therapy and was also given chloramphenicol, 1 g. daily. There was dramatic improvement in exercise tolerance, and all abnormal signs in the chest disappeared within a few days. The radiographic changes disappeared completely by the end of three weeks. The pulmonary function studies repeated after 10 days of treatment showed improvement in every respect. The case has been reviewed regularly since her discharge a month later on a small maintenance dose of cortisone (37.5 mg.). Her general health has remained excellent, and no abnormalities were seen in chest radiographs. The finger clubbing has completely disappeared but the serum proteins showed no essential change in the previous abnormal pattern.

W. GROBIN

Effects of Morphine and Other Drugs on Motility of the Terminal Ileum.
E. E. DANIEL, W. H. SUTHERLAND AND A. BOGOCH: *Gastroenterology*, 36: 510, 1959.

Ileal motility was studied in four patients at various intervals after colectomy by introducing a balloon into the stomal opening of the ileostomy. The balloon was attached to a polyethylene tube which led to a manometer. After establishing a base line of motility the effect of adrenergic amines (norepinephrine, epinephrine, and phenylephrine) and of morphine, meperidine and other drugs was studied. Similar studies were carried out on dogs and in some cases rabbits, guinea pigs and rats. *In vitro* studies were carried out on intact pieces of human ileum and on animal intestine rapidly isolated after the animal had been killed. The significance of various types of wave patterns of ileal activity found in these studies is discussed, and the failure to find Type 4 waves recorded by other workers is mentioned.

The results of these studies confirm other work showing that atropine blocks the response to eating and also morphine-induced spasm; the latter is not influenced by complete vagotomy. These findings suggest that morphine has a direct action on some elements in the wall of the intestine itself, probably the nervous elements of the wall which are cholinergic in nature. Further study will be required to decide such other possibilities as that morphine might release or stimulate synthesis of some intestinal motor substance (acetylcholine, serotonin). It was also found that nalorphine antagonized morphine spasm in both dogs and humans and that hexamethonium did not reverse this effect in dogs. The finding that morphine did not stimulate dog or human ileum *in vitro* suggests that receptors involved *in vivo* are different from those in the *in vitro* action. The adrenergic amines inhibit intestinal activity of the human as well as the animal ileum, which suggests that stress-induced intestinal hypermotility cannot be due to increased sympathetic activity.

W. GROBIN

INDUSTRIAL MEDICINE

Clinical Toxicology in Occupational Medicine.
R. T. JOHNSTONE: *J. Occup. Med.*, 1: 12, 1959.

The clinical toxicologist has an important role in occupational medicine, his primary task being the recognition and disposition of occupational diseases. He practises as a searcher for facts, which must fit into a framework of sequence and consequence. Attainment of this pattern through utilization of the background of internal medicine with certain tools and technique is discussed.

The need in industry is for a comprehensive program of environmental medicine with major emphasis upon prevention. To be competent, the clinical toxicologist in occupational medicine should have a background training in internal medicine. Further interest and education in this field is advisable, together with training in certain areas outside the traditional boundaries of medical knowledge.

This multiphasic training includes:

(a) Gaining a knowledge of the chemistry of industrially used materials. Certain difficulties present themselves—the secrecy residing in trade name products, the sudden appearance within industry of an entirely new chemical compound, and the use of a chemical not previously considered of any economic utility. The clinical toxicologist is compelled to secure information from various sources. Personal acquaintance with the right people is of importance.

(b) In-plant education. Complete understanding of a given process is an important aid to diagnosis.

(c) Experience in interpreting x-ray films of the chest, beyond that ordinarily possessed by an internist.

Reference is made also to sources of information with which the toxicologist should supplement journals and textbooks on occupational medicine and industrial hygiene. Among these are journals and texts dealing with industrial chemistry.

The consultant to whom a case had been referred for opinion has an important role. When he sees a worker during or shortly after his illness, he serves best the worker, the employer and the insurance carrier if he fulfils the traditional ideas of physician-patient relationship. On the other hand, a case seen months or more after the alleged onset of an occupational disease is, while in litigation, one in which the consultant's opinion should be transferred directly to the referring agency.

MARGARET H. WILTON

BOOK REVIEWS

CRUSADER UNDAUNTED. Dr. J. C. Geiger, Private Physician to the Public. Max S. Marshall. 246 pp. The Macmillan Company, New York; Brett-Macmillan Ltd., Toronto, 1958. $3.50.

This book is entertaining and instructive as a description of the career and activities of a public health officer. It tells little about Dr. Geiger himself beyond a biographical thread that runs through it. The early chapters that are exclusively biographical are written in a rather jerky style like that of a radio commentator introducing an after-dinner speaker; however, in succeeding chapters describing incidents in Dr. Geiger's career, the subject takes command and the book is easier to read. There is a dearth of dates and a deal of discursiveness; chronological order is not followed.

Dr. Geiger was born in Alexandria, Louisiana, in 1885 and was educated in New Orleans. Yellow fever was endemic there and he was introduced to public health measures as a student, employed to seek and take mosquitoes, and destroy their breeding places in the backyards of the city. He survived the resulting yellow fever, and went on to graduate successively in chemistry, microbiology and medicine, at Tulane, taking his D.P.H. in 1919. He became a pathologist at the University of California under Dr. Glanville Rusk, and later an epidemiologist in the United States Public Health Service. Finally, he served with various municipal public health departments, notably in Chicago and San Francisco. The chapter on Chicago is particularly colourful.

Altogether, the book gives an excellent picture of the qualities required of a good medical officer of health in his relations with the politicians, the public and the practising profession; it says little about Dr. Geiger's scientific contributions or his personal life. It contains much that is interesting and useful for the orientation of anyone about to embark in public health as a career, and shows that many of the more important problems in that field result, not so much from the diseases that man has to fight, as from his own cussedness as an organized animal.

NUTRITION IN HEALTH AND DISEASE. Lenna F. Cooper and others. 734 pp. Illust. 13th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1958. $6.00.

This book, which is frequently used as a text by training schools for nurses, is divided into four parts: principles of nutrition, diet in disease, food selection and preparation (including many special recipes), and food and other tables. It is up-to-date and easily readable, but rather dull. Canadian readers should remember that one American quart, as used in this book, is about equal to one pint and a half in Canadian measures. On page 95 it is stated that a three-ounce serving of meat, fish or fowl adds 4815 units of vitamin A to the day's meals. As the "muscle meats", beef, lamb, pork, veal and chicken, contain no vitamin A and few fish contain even one-tenth of this amount, this statement is hard to understand. On page 222 it is explained that the figure of 4815 had been arrived at by assuming that liver, which contains enormous amounts of this vitamin, would be eaten every ten days. This is a large assumption and certainly should have been stated earlier.

The book contains a great deal of reliable information which would be useful to physicians.

BATTLE FOR THE MIND: A PHYSIOLOGY OF CONVERSION AND BRAIN-WASHING. William Sargant. 217 pp. Illust. Pan Books Ltd., London, 1959. 2s. 6d.

A very frightening but rather necessary book, first published by a London psychiatrist in 1957, has recently appeared in this paperback edition, and there is therefore no excuse for its neglect by any educated person. Its subject, the manipulation of people, concerns us all very closely; in view of the current battle of ideologies, with the prize no less than the mastery of the entire world, any study of the techniques by which ideas are implanted and firmly rooted in the minds of the people, or displaced by another set of ideas, cannot fail to be of interest. Dr. Sargant shows how through the ages certain principles have been cleverly applied to religious and political indoctrination. He begins his book with an outline of the scientific basis of animal and human behaviour, pointing out the sad neglect in the western world of Pavlov's writings on psychology, and then describes the various treatments available to change psychotic and neurotic ideas. From this, it is a simple step to a discussion of the techniques of religious conversion, and in this chapter Dr. Sargant points out the comparative failure of intellectual methods and the success of intensely emotional approaches to religion. He then deals with political indoctrination and brainwashing techniques, relating from time to time the facts in these fields with the original Pavlovian work on conditioned reflexes.

What is urgently needed of course is a sound knowledge of the defences against brainwashing, and Dr. Sargant has a word to say on this topic too. He indicates that the captive faced with a series of sessions of brainwashing must find his safety in an absolute refusal to co-operate with his captors or to

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become emotionally involved. He also indicates the value of a sense of humour.

This book is beautifully written, and has the advantage of an additional chapter by Robert Graves on brainwashing in ancient times. It is recommended reading for all those who are puzzled about the world situation.

A HISTORY OF MEDICINE IN SOUTH AFRICA UP TO THE END OF THE NINETEENTH CENTURY. Edmund H. Burrows. 389 pp. Illust. Published under the auspices of the Medical Association of South Africa. A. A. Balkema, Cape Town and Amsterdam, 1958.

This well-written history, commissioned by the Medical Association of South Africa, gives a most interesting and detailed account of medicine in South Africa, from the early days of the Dutch East India Company to about 1900. Under the Dutch East India Company, the first Commander of the settlement was Johan van Riebeeck, a surgeon, who became an administrator of the Company, arriving at the Cape of Good Hope in 1652. His original minute of instruction from the Company read: "It has been thought fit to establish a rendezvous on the shores of Cabo Bona Esperance in order that our passing ships may safely touch there to obtain meat, fresh vegetables, water and other necessaries, and that our sick may be restored to health."

With the Huguenots also came their surgeons, including the progenitors of well-known South African families, such as Jean Prieur du Plessis (1638-1708).

In 1795 the Dutch capitulated to the British, and from this time onwards English and Scottish physicians came into the country. With the British forces, a number of German surgeons and physicians also came to settle. One of the most interesting figures at the Cape was James Barry, M.D. (Edinburgh 1812), subsequently found to be a woman, who rose to high office in the British Army.

It is instructive to note that general anæsthesia was introduced into South Africa very soon after its use in America and Europe. Dr. W. G. Atherstone amputated the leg of the deputy sheriff of Albany, in Grahamstown in 1847, using ether. When a sailing vessel from America brought news to the Cape in 1847 of Morton's use of ether as an anæsthetic agent in Boston in 1846, Atherstone decided to use this substance. He was unacquainted with Simpson's work in Edinburgh.

Mentioned in this book is an interesting link with a well-known Canadian medical scientist, Professor E. G. D. Murray, whose father, Dr. G. A. E. Murray, was one "whose name will always stand in the medical history of Johannesburg".

CHIRURGIE DER LEBER: Klinik und Technik (Surgery of the Liver; Clinical Features and Techniques). M. Reifferscheid, Bonn, W. Germany. 168 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1957. DM 46.

This monograph on the surgery of the liver is based upon the author's personal studies and upon an extensive acquaintance with the world literature. It begins with a description of the anatomy and topography of the liver, to which the author's personal investigations have made substantial contributions. He then discusses the clinical features of those disorders of the liver which are amenable to surgical procedures, together with the diagnostic studies necessary before operation and the preparation of the patient for operation. The greater portion of the monograph is devoted to operative technique, with full treatment of liver resection, liver abscess and echinococcal cyst. Portocaval anastomosis is not included. A short section on after-treatment is followed by a final survey, taken from the world literature, of the results of operative treatment of liver disorders. The book is well illustrated and has a good bibliography.

NEOPLASTIC DISEASE AT VARIOUS SITES. Vol. II, Tumours of the Bladder. Edited by David M. Wallace. 352 pp. Illust. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1959. $10.25.

Volume II of the series "Monographs on Neoplastic Disease at Various Sites" is concerned with tumours of the bladder. The aim of the monograph is eventually to cover neoplastic disease of each organ in an extremely complete fashion. This is indeed true of this volume. Fourteen authors, each an authority in this field, have contributed to this work.

It begins with a statistical survey of bladder cancer in the British Isles, and compares these figures with the incidence in other lands. It is pointed out that there is a definite increase in the death rate from this disease in males.

The industrial risk of bladder cancer is fully discussed; it presents a definite menace in industries using organic dyestuffs, rubber, and certain other chemicals. This section is remarkably complete, going so far as to include the procedure for claiming disability benefits in England.

Concepts of the etiology of bladder cancer are reviewed. Pathology and the classification of tumour grade are treated comprehensively.

Treatment is thoroughly discussed, and this section is divided into surgical therapy and radiotherapy. Recent concepts concerning the use of bowel in this type of surgery are discussed, and an entire chapter is devoted to the biochemical changes resulting from uretero-intestinal anastomosis. The British are masters in the use of radiotherapy for cancer, and maintain their reputation in this book. It concludes with an analysis of the results of treatment, and survival rate. The book fulfils its purpose in completely covering the subject, and may be accepted as the current authoritative text on cancer of the urinary bladder.

THIRST. Physiology of the Urge to Drink and Problems of Water Lack. A. V. Wolf, Walter Reed Army Medical Center, Washington, D.C. 536 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1958. $13.75.

Man's need for water has been recognized for centuries, and thirst is recognized as the physiological signal of water deficit. In spite of this, the cause of the sensation has never been clearly understood, and it is only recently that large-scale studies of dehydration under varying climatic conditions have been undertaken.

This volume is a monumental review, but the literature has been critically surveyed, so that it constitutes a useful and authoritative textbook. In the second section original accounts of experiences of dehydration and thirst are reproduced, including some of the desert trials in which the author participated. The volume will be found of great value as a standard reference work by all those who are interested in the physiology of thirst.

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STATUS THYMICOLYMPHATICUS: A Nutritional Endocrine Syndrome. 48 pp. W. N. Kemp, Vancouver, 1959.

The theme of this brochure is best summarized in the author's own words in his concluding paragraphs:

"1. Fetal death, asphyxia and atelectasis of the newborn, pneumonia and diarrhœa of the newborn are all considered to be clinical instances of a severe dysfunction of the pituitary-thyroid-adrenal axis in a fetus or an infant whose mother's diet has been grossly lacking in iodine in the last trimester of pregnancy.

"2. Status thymicolymphaticus likewise is of similar origin but of a degree which permits a live birth. In this syndrome, whether or not an infant lives to the relatively safe age of two years, depends entirely upon the fortuitous, or otherwise, combination of the following factors: the degree or degrees of deficiency in the diet of iodine and/or vitamin C, and the incidence of internal or environmental stresses.

"3. The validity or otherwise of this hypothesis can be experimentally tested by some suitable modifications of the classical physiologic experimental work of Crowe and Wisloki (1914)."

Copies of the brochure may be obtained by writing to the author, Dr. W. N. Kemp, at 2414 Main Street, Vancouver 10, B.C.

GRUNDRISS DER PERKUSSION UND AUSKULTATION (The Basis of Percussion and Auscultation). Prof. G. Landes. 132 pp. Illust. Walter de Gruyter & Co., Berlin, 1958. DM 9.80.

In this small volume the author presents an outline of percussion and auscultation for the medical student. In the first part, the historical development and technique of these methods of examination are described. A chapter on the examination of pulse and blood pressure is included. In the second part of the book the findings on percussion and auscultation in diseases of the lungs are discussed under the following headings: diseases of the bronchi, diseases with increased air content (emphysema), diseases with decreased air content (infiltrations, atelectasis), diseases with cavity formation in the lungs, abnormal conditions in the pleural space (effusion, pneumothorax). Similarly the diseases of the cardiovascular system are described, and a special chapter is devoted to the congenital heart diseases.

The text is clearly written and there are some instructive illustrations. The bibliography is scanty and considers only the German literature.

HOSPITAL AND COMMUNITY. History of the Royal Melbourne Hospital. K. S. Inglis. 226 pp. Illust. Melbourne University Press, Victoria, Australia; The Macmillan Company of Canada Limited, Toronto, 1958. $5.00.

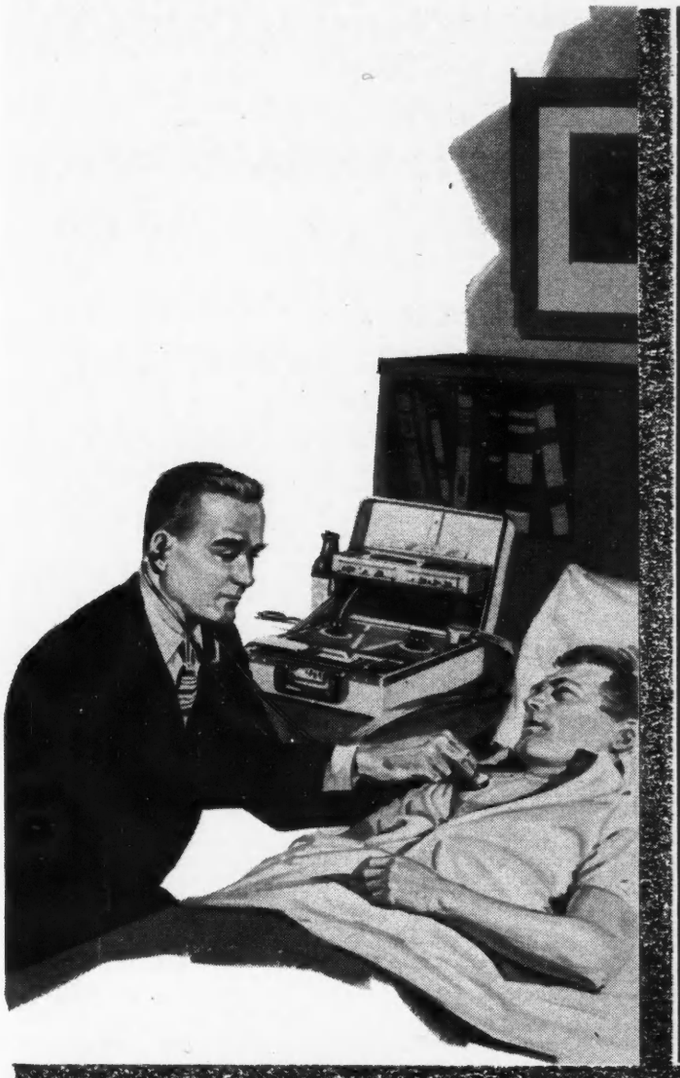
The Royal Melbourne Hospital, one of Australia's most famous medical institutions, had its origins in 1841 when a group of private citizens called a public meeting to consider fund-raising for the provision of a hospital in the new town. They had previously sought, and failed to obtain, government funds for the project, and the main theme of Inglis's most admirable history of the hospital is the interplay of private charity and the state in the financing and control of a necessary medical facility.

As a history of a great hospital, told with wit and intelligence, it must rank high. As a social document it will also be of interest to a wide range of readers for its objective discussion of many issues connected with medical care.

For the first 50 years of its life the hospital seems to have been a centre of controversy. For 40 years discussion raged over its rebuilding or relocation—in the event, it was first rebuilt in 1913 and then relocated in 1944 in its present home, to which it might well have moved 70 years earlier. Other evidences of the leisurely pace of democracy are the fact that it took 25 years of agitation to get an eye department, and the even more astonishing fact that the first Melbourne professors of medicine and surgery were appointed only in 1955, 70 years after the appointments had first been suggested. In 1891, Allen, the pathologist, wanted a research institute; in 1919 it was built and now has Sir MacFarlane Burnet as its distinguished head.

The book is full of delightful detail, such as the story of the tuberculous girl who about 1880 was prescribed seven bottles of rum and 12 bottles of brandy in a 28-day stay, and the suggestion by a hostile newspaper that sensible persons should carry cards giving their name and address, and a note "If any accident should happen to me, do not on any account take me to the Melbourne Hospital." This pre-Listerian attitude had its justification, for in 1870 a Melbourne doctor said that no one with the least experience of disease could doubt that a patient at home had a far better chance of recovery than in hospital. One of the reasons for increased use of modern hospitals is, as Inglis points out, the gradual abandonment of the public attitude of fear of them.

In spite of the remoteness of the setting, anyone interested in hospitals will find something entertaining and instructive in this well-written historical monograph.



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Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Vision Screening for Elementary Schools. The Orinda Study. Henrik L. Blum, Henry B. Peters and Jerome W. Bettman. 46 pp. Illust. University of California Press, Berkeley and Los Angeles, 1959.

Volunteer and the Psychiatric Patient. Report of the Conference on Volunteer Services to Psychiatric Patients held in Chicago, Illinois, June 12-17, 1958. 123 pp. American Psychiatric Association, Washington, D.C., 1959.

Insulin Treatment in Psychiatry. Edited by Max Rinkel and Harold Himwich. 386 pp. Illust. Philosophical Library, New York, 1959. $5.00.

Analgésie psychologique en obstétrique (Psychological Analgesia in Obstetrics). Edited by P. Aboulker, L. Chertok and M. Sapir. 172 pp. Pergamon Press, London and New York, 1959. $9.00.

DDT, The Insecticide Dichlorodiphenyltrichloroethane and its Significance. Edited by Paul Mueller. Vol. II. Human and Veterinary Medicine. Edited by S. W. Simmons. 570 pp. Illust. Birkhaueser Verlag, Basel and Stuttgart, 1959. Swiss fr. 66.-

Zur Begutachtung der Blutkrankheiten. (Compensation Assessment in Blood Disorders). O. Fresen, H. Begemann and H. Merker. 142 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. DM 19.50.

Miscellaneous Notes (Second Series). F. Parkes Weber. 20 pp. H. K. Lewis & Co. Ltd., London, 1959. 5s.

Chirurgie der Hand. Atlas der Operationstechnik (Surgery of the Hand. Atlas of Operative Technique). M. Iselin (Consultant Surgeon, American Hospitals, Paris), Luc Gosse, Serge Boussard and Daniel Benoist. 325 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. DM 69.-

Speech and Brain-mechanisms. Wilder Penfield and Lamar Roberts. 279 pp. Illust. Princeton University Press, Princeton, N.J., 1959. $6.00.

Autolyse-Krankheiten in der Chirurgie (Autolytic Diseases in Surgery). L. Kolowski. 160 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $4.70.

Postural Drainage and Respiratory Control. E. Winnifred Thacker. 62 pp. Illust. 2nd ed. Lloyd-Luke (Medical Books) Ltd., London, 1959. 10s. 6d.

Medical Science and Space Travel. William A. Kinney. 149 pp. Illust. Franklin Watts, Inc., New York, 1959. $3.95.

Lokalanaesthesie und Lokalanaesthetika. (Local Anæsthesia and Local Anæsthetics). H. Killian. 770 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $36.65.

Der Biologisch-Anthropologische (Existentielle) Aufbau der Persoenlichkeit (The Biological and Anthropological (Existential) Structure of Personality). G. Ewald. 67 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $2.35.

Food Inspection Notes. Harry Hill and Ernest Dodsworth. 128 pp. Illust. 5th ed. H. K. Lewis & Co. Ltd., London, 1959. 10s. 6d.

The School Health Service. S. Leff and Vera Leff. 316 pp. Illust. H. K. Lewis & Co. Ltd., London. 30s.

Immunopathologie (Pathology of Immunity). 1st International Symposium. Edited by Pierre Grabar, Paris, and Peter Miescher, Basel. 520 pp. Illust. Benno Schwarz & Co., Basel/Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $16.25.

Die Speicheldruesen des Menschen, Anatomie, Physiologie und Klinische Pathologie (The Human Salivary Glands, Anatomy, Physiology and Clinical Pathology). S. Rauch. 506 pp. Illust. Georg Thieme, Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $18.80.

Die Behandlung von Hiatushernien und Refluxoesophagitis mit Gastropexie und Fundoplicatio (Treatment of Hiatus Hernia and Reflux Œsophagitis by Gastropexy and Fundal Plication). R. Nissen and M. Rossetti. 153 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $11.80.

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The Management of Oral Disease. Joseph Bernier. 876 pp. Illust. 2nd ed. The C. V. Mosby Company, St. Louis, Mo., 1959. $15.00.

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The Essentials of Roentgen Interpretation. Lester W. Paul and John H. Juhl. 839 pp. Illust. Paul B. Hoeber Inc., Medical Book Department of Harper & Brothers, New York, 1959. $25.00.

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Studies on the Distribution and Fate of C^{14} and T-Labelled p-Aminosalicylic Acid (P A S) in the Body. Acta Radiologica Supplementum 175. Ake Hanngren. 118 pp. Illust. Acta Radiologica, Stockholm, 1959. Sw. Kr. 25.-

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Cineradiographic Studies on the Fallopian Tubes in Rabbits. Acta Radiologica Supplementum 176. Lars Bjoerk. 54 pp. Illust. Acta Radiologica, Stockholm, 1959. Sw. Kr. 25.-

The Innervation of Muscle: A Biopsy Study. C. Coers and A. L. Woolf. 149 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $10.75.

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International Work in Bilharziasis 1948-1958. 59 pp. World Health Organization, Geneva, 1959. $0.30.

Der Arbeits und Trainingseinfluss auf Kreislauf und Atmung. Eine Klinische und Physiologische Betrachtung (Effects of Work and Training on Circulation and Respiration. Clinical and Physiological Considerations). W. Hollmann. 202 pp. Illust. Dr. Dietrich Steinkopff Verlag, Darmstadt, 1959. DM 35.-

Notification of Communicable Diseases. 51 pp. World Health Organization, Geneva, 1959. $0.70.

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Die Helldunkel-Deutungen im Psychodiagnostischen Experiment von Rorschach (Interpretations of Light and Dark in the Rorschach Test). Hans Binder. 127 pp. Hans Huber, Bern and Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. DM 12.-

Physiology of Cardiac Surgery. Frank Gollan. 96 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.00.

The Treatment and Prevention of Reading Problems. Carl H. Delacato. 122 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.00.

Pancreatitis. A Clinical—Pathologic Correlation. Herman T. Blumenthal and J. G. Probstein. 379 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $10.50.

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Clinical Orthopedics. Edited by Anthony DePalma, 393 pp. Illust. J. B. Lippincott Company, Philadelphia and Montreal, 1959. $7.50.

Community Mental Health. Margaret C. L. Gildea, Washington University School of Medicine. 169 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $5.50.

Bronchography. C. Dijkstra, Medical Superintendent of De Klokkenberg Sanatorium, Breda, Netherlands. 157 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $11.50.

Allergic Encephalomyelitis. Edited by Marian W. Kies and Ellsworth C. Alvord. 576 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $14.75.

Peripheral Vascular Diseases. Travis Winsor, University of Southern California School of Medicine. 845 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $18.25.

A Guide to Orthopædics. T. T. Stamm, Guy's Hospital. 115 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $3.75.

Genetics, Radiobiology and Radiology. Proceedings Mid-Western Conference. Wendell G. Scott and Titus Evans. 149 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $6.00.

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Clinical Neurophysiology. John Marshall, Reader in Clinical Neurology, University of London, England. 296 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1959. $9.50.

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The Treatment of Diabetes Mellitus. Elliot P. Joslin and others. 798 pp. Illust. 10th ed. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1959. $16.50.

Pathology. Peter Herbut, Jefferson Medical College Hospital, Philadelphia. 1516 pp. Illust. 2nd ed. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1959. $18.50.

Dégénérescence hépato-lenticulaire (Hepato-lenticular Degeneration). G. Boudin et B. Pepin. 250 pp. Illust. Masson et Cie, Editeurs, Paris, 1959. fr. 3.500.-

Tumeurs bénignes des os. (Benign Tumours of Bones). A. Trifaud et H. Bureau. 280 pp. Illust. Masson et Cie, Editeurs, Paris, 1959. fr. 4.200.-

Les cavités cardiaques (The Heart Chambers). E. Henry, P. Courbier et P. Crochu. 176 pp. Illust. Masson et Cie, Editeurs, Paris, 1959. fr. 3.200.-

Le risque opératoire en chirurgie bilio-pancréatique (Operative Risks in Surgery of the Biliary Tract and Pancreas). Yves Salembier. 260 pp. Illust. Masson et Cie, Paris, 1959. fr. 2.500.

Obnubilation, Comas et Stupeurs (Obfuscations, Comas and Stupors). H. Fischgold and P. Mathis. 124 pp. Illust. Masson et Cie, Paris, 1959. fr. 3.000.

Angiocardiopneumographie élargie méthode d'opacification vasculaire générale par voie veineuse (Extended Angio-cardiopneumography). P. Viallet and others. 110 pp. Illust. Masson et Cie, Paris, 1959. fr. 4.400.

Schizophrenia. An Integrated Approach. Edited by Alfred Auerback. 224 pp. The Ronald Press Company, New York, 1959. $5.50.

Anatomy of the Human Body. R. D. Lockhart, G. F. Hamilton and F. W. Fyfe. 697 pp. Illust. Faber & Faber Limited, London; British Book Service (Canada) Ltd., Toronto, 1959. $18.90.

A B C fuer Zuckerkranke (A B C for Diabetics). F. Bertram. 88 pp. Illust. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1959. $1.00.

Microbiology Yesterday and Today. Edited by Vernon Bryson. 122 pp. Illust. Institute of Microbiology, Rutgers, The State University

Proceedings of the Tenth Annual Conference on the Nephrotic Syndrome. Edited by Jack Metcoff. 282 pp. Illust. Sponsored by the National Kidney Disease Foundation, New York.

A Way of Life and other selected writings of Sir William Osler. 278 pp. Illust. Dover Publications Inc., New York, 1959. $1.50.

Elementary Statistics with Applications in Medicine and the Biological Sciences. Frederick E. Croxton. 376 pp. Illust. Dover Publications Inc., New York, 1959. $1.95.

Ciba Foundation Symposium on Carcinogenesis. Mechanisms of Action. G. E. W. Wolstenholme and Maeve O'Connor. 336 pp. Illust. Little, Brown and Company, Boston, Mass., 1959. $9.50.

Pocket Book of Proprietary Drugs. Cruikshank and Stewart, Edinburgh, Scotland. 236 pp. The Macmillan Company of Canada Limited, Toronto, 1959. $1.80.

Lehrbuch der Haut und Geschlechtskrankheiten (Textbook of Skin and Venereal Diseases). Dr. Walther Schoenfeld, Professor and Head of University and Polyclinic for Skin and Venereal Diseases, Heidelberg, Germany. 546 pp. Illust. 8th ed. Georg Thieme, Stuttgart, Intercontinental Medical Book Corporation, New York, 1959. D.M. 49.50.

Notable Names in Medicine and Surgery. Hamilton Bailey and W. J. Bishop, London, England. 216 pp. 3rd ed. H. K. Lewis & Co. Ltd., London, 1959. £1. 15s.

Clinical Involvements. H. Gardiner-Hill, Consulting Physician to St. Thomas's Hospital, London, England. 200 pp. Illust. Butterworth and Co. Ltd., London, England; Butterworth & Co. (Canada) Ltd., Toronto, 1958. $6.50.

Arthritis. General Principles, Physical Medicine, Rehabilitation. Edward W. Lowman, Associate Professor of Physical Medicine and Rehabilitation, New York University College of Medicine. 292 pp. Illust. Little, Brown and Company, Boston; J. B. Lippincott Company, Montreal, 1959. $9.50

Low Intensity Radium Therapy. Charles L. Martin, Clinical Professor of Radiology, Dallas, and James A. Martin, Associate Professor of Radiology, Southwestern Medical School of the University of Texas, Dallas. 257 pp. Illust. Little, Brown and Company, Boston and Toronto, 1959. $12.50.

Mechanisms of Hypersensitivity. J. H. Shaffer, Henry Ford Hospital, Detroit, Mich., and Merrill W. Chase, The Rockefeller Institute for Medical Research, New York. 754 pp. Illust. Little, Brown and Company, Boston and Toronto, 1959. $18.50.

Radiodiagnostic en otologie (Roentgen Diagnosis in Otology). Michel Portmann, Medical Faculty, Bordeaux, France, and Georges Guillen, Head of the Clinic, Medical Faculty, Bordeaux, France. 207 pp. Illust. Masson & Cie, Paris, France, 1959. 3.700 FF.

Released Mental Patients on Tranquilizing Drugs and the Public Health Nurse. Ida Gelber, Ed.D., R.N., Research Consultant, New York City Department of Health, Office of Research and Development. 139 pp. New York University Press, New York, 1959. $3.00.

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PICKWICK, S., *Textbook of Medicine*, Jones and Jones, London, 1st ed., p. 30, 1955.

Illustrations: Photographs should be glossy prints, unmounted and untrimmed, preferably not larger than 10 by 8 inches. Colour work can be published only at the author's expense. Magnification of photomicrographs must always be given. Photographs must not be written on or typed on. Identification can be made by pasting an identifying legend on the back. Patients must not be recognizable in illustrations, unless the written consent of the subject to publication has been obtained. Graphs and diagrams should be drawn in india ink on suitable white paper. Legends to all illustrations should be typed separately from the text of the article. Illustrations should not be rolled or folded.

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LOCUM WANTED in Ontario for the months of October and November by male physician, age 34, married, writing certification in internal medicine. Wide experience in electrocardiography. Please reply to Box 420, CMA Journal, 150 St. George St., Toronto 5, Ont.

SCOTTISH GRADUATE, 1950; L.M.C.C., 1955, age 32 years, married, now completing 4 year residency in general surgery in United States, seeks opening with surgeon, group or clinic. Available July, 1960. Reply to Box 421, CMA Journal, 150 St. George St., Toronto 5, Ont.

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MEDICAL NEWS *in brief*

(Continued from page 498)

NINTH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT

The Ninth Annual Instrument Symposium and Research Equipment Exhibit, sponsored by research equipment manufacturers and the Washington sections of six scientific societies, will be held from September 28 to October 1 at the National Institutes of Health, Bethesda, Maryland. The equipment display, valued at more than $800,000, will feature new developments in electronics, laboratory glassware, and surgical, optical, radiation, and gas-sampling instruments. The products of 103 manufacturers will be exhibited. All professional and technical persons are invited to view the exhibits and to attend the symposium on recent developments in research methods and instrumentation.

Dr. James A. Shannon, director of the National Institutes of Health, will open the symposium on September 28 at 8 p.m. A panel discussion of pressing topics in instrumentation will be led by Dr. Ralph H. Muller, in charge of special instrumentation problems at the Los Alamos National Laboratory. Dr. Van Zandt Williams, director of research, Perkin-Elmer Company, Norwalk, Conn., and Dr. Lawrence T. Hallett, editor of *Analytical Chemistry*, Washington, D.C., will also participate. A well-known speaker on biophysics, Dr. Alexander Kolin, of the University of California at Los Angeles, will lecture on electromagnetophoresis at 2:00 p.m. on September 29. A demonstration of the phenomenon will be given. Gas chromatography will be discussed at a symposium session on September 29 at 8 p.m. in the Clinical Center Auditorium. Dr. Evan C. Horning, chief of the Laboratory of Chemistry of Natural Productions, National Heart Institute, is chairman of the session. The other symposium topics are scheduled for September 30, at 2:00 and 8:00 p.m. and October 1, at 2:00 p.m. An outstanding group of speakers, all specialists in their fields, have been invited to present papers on serum agar methods, irradiation of cells in tissue culture, and on nuclear and electronic magnetic resonance.

The professional societies sponsoring the symposium are the American Association of Clinical Chemists, American Chemical Society, Instrument Society of America, Professional Group on Medical Electronics of the Institute of Radio Engineers, Society of American Bacteriologists, and the Society for Experimental Biology and Medicine.

Further information from James B. Davis, National Institutes of Health, Public Health Service, Bethesda 14, Maryland.

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STUDIES IN TRICHOMONIASIS

Following the symposium on human trichomoniasis held at Reims in May 1957, a conference of international representatives was called under the chairmanship of Dr. Gaston Chappaz. This resulted in the formation of an international group to maintain interest and to pursue further studies in this field. The Groupe International d'Etudes de la Trichomonase Humaine (G.I.E.T.H.) has been constituted a permanent commisssion under the auspices of the Union Internationale contre le Péril Vénérien et les Tréponématoses with headquarters at l'Institut Alfred Fournier, Paris. The objectives of the study group are: (1) To set up an international registry of research workers especially interested in the field of human trichomoniasis. (2) To promote international scientific meetings. G.I.E.T.H. has participated in the organization of the First Canadian Symposium on Non-gonococcal Urethritis and Human Trichomoniasis to be held in Montreal, September 21-22, 1959 (Secretary, Dr. Z. Gallai, 8580 Esplanade, Montreal 11, Quebec). (3) To aid in the publication of original articles or their abstracts in the various foreign journals. (4) To assist the various research workers in contacting the many public and private organizations for grants.

All research workers and other persons particularly interested in this field are urged to become members of this organization by sending the following information to G.I.E.T.H., Institut Alfred Fournier, 25 Boulevard St-Jacques,

(Continued on page 70)

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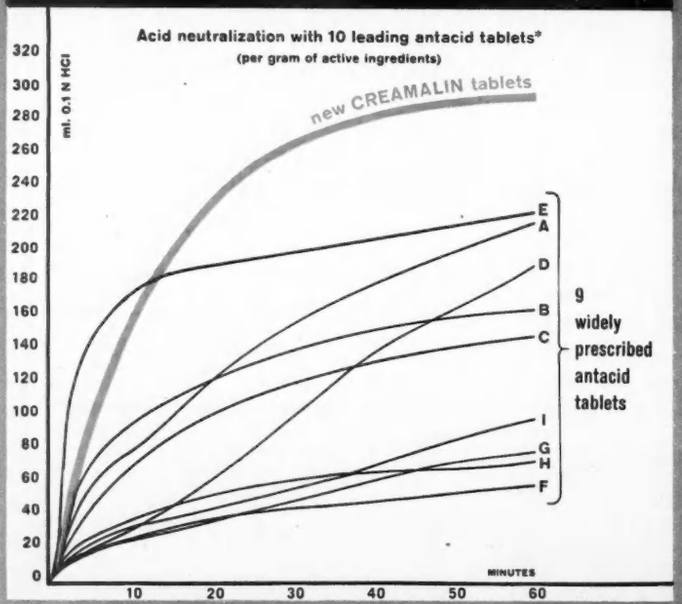
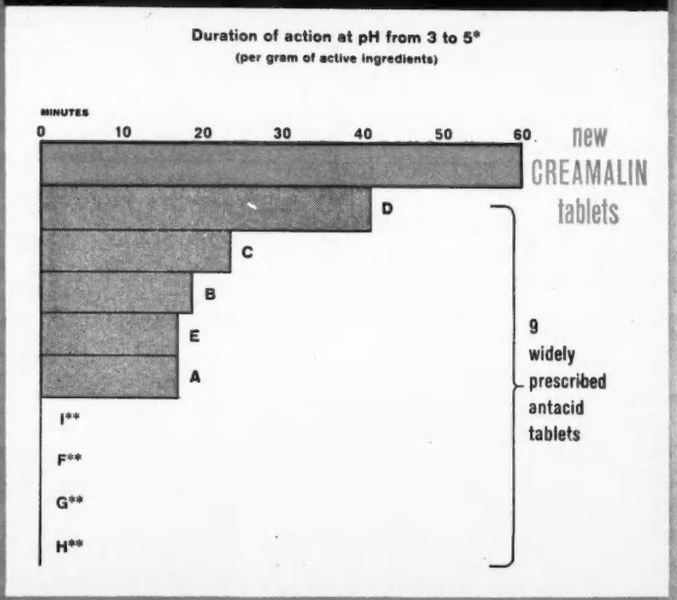


Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

CREAMALIN NEUTRALIZES *MORE* ACID *LONGER*

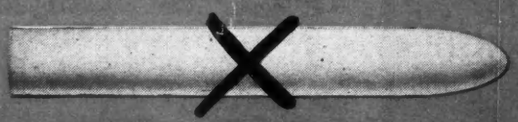
More Lasting Relief



*Hinkel, E. T., Jr., Fisher, and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
**pH stayed below 3.

Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydroxide.

1. *Neutralizes acid faster (quicker relief)*
2. *Neutralizes more acid (greater relief)*
3. *Neutralizes acid longer (more lasting relief)*
4. *No constipation • No acid rebound*
5. *More pleasant to take*



No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

Adult Dosage: Gastric hyperacidity—2 to 4 tablets as necessary. Peptic ulcer or gastritis—2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

Winthrop LABORATORIES • NEW YORK 18, NEW YORK

MEDICAL NEWS *in brief*

(Continued from page 63)

Paris XIV^{e}, France: (a) name and address; (b) present university and/or hospital appointments; (c) bibliography of publications relative to the subject—trichomoniasis; (d) current interests and investigations.

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JOHN S. McEACHERN MEMORIAL FELLOWSHIPS

Applicants for the John S. McEachern Memorial Fellowships must be graduates in medicine of an approved Faculty of Medicine or hold an advanced degree in physics from an approved Faculty of Graduate Studies; and (a) shall have already pursued postgraduate study in a field related to the diagnosis or treatment of cancer; (b) shall be endorsed by one of the Faculties of Medicine in Canada in order to augment the clinical anti-cancer program in the geographic area of its major influence; (c) shall under this Fellowship pursue further postgraduate study related to the diagnosis or treatment of cancer acceptable to the Advisory Committee on Fellowships of the Canadian Cancer Society; and (d) shall express a firm interest and assume the moral obligation to return to practise their profession subsequently in Canada with a particular interest in cancer, preferably in the sphere of influence of the endorsing Faculty of Medicine.

It is considered that the special study for which a Fellowship is requested shall be that for which opportunities are not already available within the endorsing Faculty or affiliated teaching hospitals.

These Fellowships have an approximate value of $10.00 a day and are tenable for a maximum period of one year. An additional award at the rate of $400 per annum will be made to married Fellows. At the discretion of the Advisory Committee on Fellowships additional amounts may be made available for travelling expenses. Application forms may be obtained through the Dean of the respective Faculty of Medicine, from the Canadian Cancer Society, 800 Bay Street, Toronto 5, Ont.

Applications should be submitted to the above address not later than October 1 in any year.

—

NATIONAL IMMUNIZATION WEEK

During the week of September 20, National Immunization Week will be celebrated in Canada for the 17th consecutive year. This event is sponsored by the Health League of Canada in co-operation with health departments. During the week, the Health League will try to make it possible for every citizen in Canada to learn why every child should be protected against diphtheria, whooping cough, tetanus, poliomyelitis and smallpox. Great strides in the control of disease have been made through immunization, but the League believes that it is only through repeated reminders that Canadians will take advantage of immunization and safeguard their families.

PRIMARY MYOGLOBINURIA

A 19-year-old man was admitted to hospital with a three-day history of muscle pain, tenderness and stiffness, together with the passage of dark, reddish-brown urine. These symptoms developed during strenuous calisthenics and became worse after each ensuing period of these exercises until finally on the third day the muscles became very painful, swollen, hard and tender. The urine became dark and diminished in quantity. The laboratory findings were essentially within normal limits except for the urine, which contained 100 mg. of albumin per 100 ml., and whilst there were only 4-5 red blood cells in the sediment the guaiac reaction was four-plus. In the plasma the guaiac reaction was also four-plus, although the plasma was normal in colour. By the fifth hospital day there was marked improvement in urinary output, and after one week the urine was lighter in colour. The pain and tenderness and stiffness disappeared after three weeks. A thorough check-up 20 days after the onset of this illness failed to reveal any significant findings in urine, blood or renal function tests. The only positive finding was small foci of infiltration with lymphocytes and plasma cells in muscle biopsy specimens. The blood pressure which was slightly elevated on admission quickly dropped and remained normal. After discussing differential diagnosis, the author warns of the danger of inducing an attack of myoglobinuria by strenuous exertion, as any attack is potentially fatal. — R. L. Gillett, *New England J. Med.*, 260: 1156, 1959.

—

OBSTRUCTIVE AIRWAY DISEASE

A study of pulmonary function was conducted by Capel and Smart (*Lancet*, 1: 960, 1959) on 362 patients complaining of one or more of the following: effort breathlessness, cough, expectoration and wheeze, and suffering from chronic bronchitis, chronic bronchitis and emphysema, or asthma. The effort intolerance of these patients was graded as mild, moderate, and severe. One-second forced expiratory volume (F. E. V.), a simple measure of the severity of airway obstruction, was measured in each of these patients, as well as in 34 ambulance drivers and 10 hospital domestic workers who served as controls. Scatter diagrams showed that a number of the less disabled men had a very low F. E. V. From these findings it is inferred that the effect of age and height on the F. E. V. and on effort intolerance is small compared with the effects of obstructive airway disease. By the time patients complain of more than mild effort intolerance, considerable loss of respiratory reserve is already present. The intolerance of effort appears to be proportional to obstruction of the airway.

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THE INTERNATIONAL SOCIETY FOR CLINICAL AND EXPERIMENTAL HYPNOSIS

The Canadian Division of the International Society for Clinical and Experimental Hypnosis invites

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MEDICAL NEWS *in brief*

(Continued from page 71)

application for associate and full membership. Applicants must hold an M.D., D.D.S., or Ph.D. degree from recognized universities and have had some experience in the use of hypnosis in the field of their competency.

The Canadian Division is one of 25 divisions of the International Society for Clinical and Experimental Hypnosis representing 25 countries throughout the world. Applicants should write to Dr. Morton Korenberg, Medical Arts Building, 1538 Sherbrooke St. West, Montreal, giving full particulars of training and experience in the field of hypnosis.

—

SHORT-TERM HORMONE THERAPY IN RHEUMATIC CARDITIS

Of 53 attacks of active rheumatic carditis in 47 children, 26 were presumably initial and 27 recurrent. All the patients received antibiotic medication during their entire hospital stay and were given steroids such as hydrocortisone, prednisone, prednisolone and methylprednisolone for an average period of seven days, after which this therapy was terminated abruptly. They were then observed for an additional week with modified bed rest. The criteria for diagnosing active carditis were those of the American Heart Association.

Comparison of the clinical course before and after therapy in 36 patient attacks treated early and 17 treated late is presented by Wilson and Lim (*New England J. Med.*, 260: 802, 1959). Progressive clinical manifestations of active myocarditis were arrested within 24 to 72 hours of institution of steroid therapy in all patients. Five patients required a second seven-day course of therapy a week later, and in all of the patients the progressive symptoms of carditis were terminated. All but two of the 36 patients treated early revealed no overt evidence of residual cardiac damage, whilst among the 17 patients treated late there was little evidence of improvement in the cardiac damage present at the beginning of the treatment. The response of the circulating eosinophils proved a useful guide to effective dosage in this series. No serious side effects were observed during treatment, and the abrupt withdrawal of steroids was also without complications in the majority of patients.

Congestive failure was present in all the patients in the terminal stage, and pneumonia was a complicating factor in 24. Even the earliest cases showed myocardial damage, whilst damage to the valves was only minor and did not become marked except in the cases where the duration of the process had been longer. The authors believe that in the majority of cases, if treatment is started early, effective short-term therapy may result in termination rather than suppression of carditis without overt residual cardiac damage. "Rebound" is generally considered to be a reflection of the healing phase which has been suppressed during therapy, and is not an indication for continuing therapy. It occurs four times as frequently in patients receiving short-term therapy late as in those treated

early. Reference is made to an analysis of the evolution of systolic and diastolic murmurs in 114 children with active carditis followed up for periods of six months to 20 years on symptomatic therapy. This showed that one-third of the patients lost their murmurs and that 9% lost them within six months and 15% within one year; it is significant that cardiac-chamber enlargement in these children remained uninfluenced. In the present series, all 36 patients treated early with steroid hormones showed a regression of chamber enlargement. In active carditis, short-term hormone therapy will terminate inflammatory process irrespective of its duration, but only in early treatment can residual cardiac damage be expected to be minimal. Long-term hormone therapy is probably not required.

—

CHARCOT'S ARTHROPATHY AFTER INTRA-ARTICULAR HYDROCORTISONE

Most reports stress the benefit derived by patients from intra-articular hydrocortisone and the scarcity of side reactions. It might have been expected, however, that the repeated injections could result in an aggravation of the arthritis, because freedom from pain would encourage undue weight-bearing and thereby accelerate the progress of the disease. Chandler and his colleagues (*Brit. M. J.*, 1: 952, 1959) had this experience in 10 of 18 patients given prolonged intra-articular therapy. They report the case of a 66-year-old woman, whose arthritis of the right hip-joint was treated with 50 mg. of hydrocortisone injected at approximately monthly intervals. Relief from pain lasted some three weeks on each occasion. After two years of these treatments it was found that there was a 2 in. true shortening of the right leg, and the radiograph of the right hip showed gross destruction of the femoral head and the roof of the acetabulum. This picture was indistinguishable from the condition described by Charcot. No other cause for this condition could be found, rheumatoid arthritis, tuberculosis, and other infective processes having been excluded by serological tests and biopsy. The author emphasizes the need for careful radiological supervision during prolonged treatment with intra-articular injections of steroids.

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BANTING RESEARCH FOUNDATION GRANTS

The Banting Research Foundation announces 16 new grants ranging in value from $480 to $6300 made at the annual meeting in June to medical research workers across Canada to help finance original medical research projects.

Grants were made to the following research workers: Dr. A. A. Axelrad, Division of Biological Research, The Ontario Cancer Institute, Toronto, to study chromosome analysis of virus-induced early kidney tumours in the hamster; Dr. J. V. Basmajian, Department of Anatomy, Queen's University, Kingston, to study development of electronic biocontrol apparatus for denervated muscle; Dr. Sylvia H.

(Continued on page 74)

MEDICAL NEWS *in brief*

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Bensley, Department of Anatomy, University of Toronto, to study mast cells and connective tissue lesions; Dr. E. S. Goranson, Division of Biological Research, The Ontario Cancer Institute, Toronto, to study relation of diabetes and cell growth; Dr. R. Bohkirk, Montreal General Hospital, Metabolism Laboratory, Montreal, to study hydrolysis of steroid conjugates in urine; Dr. E. A. Kallenbach, Department of Anatomy, McGill University, Montreal, to study elucidation of lymphocyte production by the thymus using labelled thymidine; Dr. W. Kalow, Department of Pharmacology, University of Toronto, to undertake studies on narcotics and addicting drugs, and also to terminate studies on aromatic esterase of human serum; Miss C. T. Laplante, Montreal Children's Hospital, to pursue studies on the functional and metabolic capacity of regenerated adrenal cortical tissue and on the role of the adrenal cortex in the etiology of adrenal regeneration hypertension; Dr. R. D. Laurenson, Department of Anatomy, Queen's University, Kingston, to study possible teratologic effects of alizarin and allied substances; Dr. T. S. Leeson, Department of Anatomy, University of Toronto, to study the development of the trachea with particular reference to cilia and cartilage as seen with the electron microscope, and to investigate the normal postnatal appearance of the hamster kidney; Mr. B. H. Messier, Department of Anatomy, McGill University, Montreal, to study turnover rate of cells; Dr. E. Pinter, Gastrointestinal Research Laboratory, McGill University, Montreal, to study fat absorption in malabsorption syndrome; Dr. J. H. Quastel, McGill-Montreal General Hospital Research Institute, Montreal, to study mechanism of acquired resistance in animals to drugs affecting the central nervous system, particularly morphine; Dr. A. Sass-Kortsak, Research Institute, Hospital for Sick Children, Toronto, to study the heterogeneity of ceruloplasmin; and Miss M. H. Wiseman, Allan Memorial Institute of Psychiatry, McGill University, Montreal, to study regulation of alternate metabolic pathways of tryptophan metabolism.

—

PROCAINE THERAPY FOR OLD AGE

Professor Anna Aslan of Bucharest, Rumania, has been claiming for some years that she obtains sensational results in arresting and reversing the aging process by giving intramuscular injections of procaine (Novocain). The New York firm of Consultants Bureau, Inc., have now furnished us with an English translation* of seven papers which appeared in *Die Therapiewoche*, by Aslan and various other physicians in Bucharest, Leipzig, Halle and Russia. Aslan began her work in May 1951, by treating 25 old people suffering from severe degenerative disease with intramuscular injections of 5 ml. of a 2% solution of procaine

*Research on Novocain in Old Age. Prof. Anna Aslan *et al.* 968 pp. Illust., Consultants Bureau, Inc., New York, 1959. $12.50.

three times a week for a series of 12 injections. This treatment was continued indefinitely in courses with 10-day intervals in between. She has now extended the treatment to large numbers of old people and also people between 45 and 60 years of age showing signs of premature aging. From her series, which has now grown to about 2500 cases, she claims that procaine acts as a "eutrophic" factor in the whole body. She says that it has a stimulating effect on the nervous system, causing memory, perception and power of concentration to return even in cases of progressive vascular disease of the brain. Œstrogen circulation begins again and hair growth is stimulated. Testicular and adrenal function improve and the cardiovascular system also improves. Bone and joint disease of a degenerative nature is favoured and there are biochemical and hæmatological changes as well.

Another of the reports translated in the brochure deals with procaine treatment of 100 old persons with degenerative joint disease, and states that continuous treatment leads to significant improvement in 26% of cases and some improvement in 60%. How much value is to be attached to all these claims may perhaps be discerned from study of the present collection of papers.

—

COURSES IN RADIOLOGICAL HEALTH

The department of industrial medicine of the New York University-Bellevue Medical Center Post-Graduate Medical School offers five courses in radiological health starting October 1959. The courses are intended for persons already trained in one of the physical, engineering, biological or medical sciences who require a comprehensive introduction to the new techniques and methods associated with radiological hazard evaluation. The courses are as follows:

Introduction to Radiological Health: Full time, October 12-23, 1959; for persons having responsibilities connected with the health and safety of personnel in installations using sources of ionizing radiation.

Radiological Health Laboratory: Full time, October 26-November 6, 1959. A series of experiments designed to furnish a familiarity with the most important categories of nuclear detection apparatus and techniques of measurement.

Radiochemical Analysis: A two-week intensive course, November 9-20, 1959, covering the techniques of radiochemistry and counting required for the determination of radioisotopes in biological and environmental samples.

Medical and Public Health Control of Ionizing Radiation: Full time, March 7-18, 1960. Primary emphasis is on the biological effects of radiation and medical control programs. Specifically designed for public health officials, physicians, and others with biological interests.

Radiation Hygiene Measurements: A four-week intensive course, April 18-May 13, 1960, offering laboratory instruction in surveying, monitoring and sampling procedures, for persons having

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MEDICAL NEWS *in brief*

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some acquaintance with nuclear measurement principles.

For further information: The Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

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LVII[e] CONGRES FRANCAIS D'OTO-RHINO-LARYNGOLOGIE

Le LVII[e] Congrès Français d'oto-rhino-laryngologie tiendra ses assises du *lundi 19 au jeudi 22 octobre 1959*, au Grand amphithéâtre de la Faculté de Médecine, rue de l'Ecole de Médecine, Paris. De nombreuses communications seront présentées et deux rapports seront discutés:

1. La chirurgie de la surdité, son état actuel, son avenir.

Rapporteurs: MM. G. Portmann, M. Portmann et G. Claverie.

2. Le laryngologiste et les données actuelles du traitement des insuffisances respiratoires aiguës.

Rapporteurs: M. Paul Aboulker avec la collaboration de J. Lissac et O. Saint-Paul.

Une exposition d'instruments chirurgicaux, d'appareillages et de spécialités pharmaceutiques intéressant l'O.R.L. se tiendra dans le Hall de la Faculté. Pour tous renseignements s'adresser au Secrétaire Général Dr. H. Guillon, 6 avenue Mac Mahon—Paris 17e, France.

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COURSES IN ARTHRITIS AND RELATED DISORDERS

The Post-Graduate Medical School of New York University-Bellevue Medical Center has announced two courses in arthritis and related disorders. The first, for general physicians, will be given November 9-13, 1959, and repeated May 16-20, 1960. This course is planned for the general practitioner who requires a basic knowledge of the field of arthritis and related disorders, including general incidence, classification, differential diagnosis, clinical manifestations, pathological characteristics, laboratory studies, and treatment. Clinic and bedside treatment will be stressed.

The second course, for the experienced clinician and research worker, will be given March 14-18, 1960. This course is designed for physicians who are familiar with the fundamental data essential for an understanding of this group of disorders. In general, applicants should have had five or more years of experience in an arthritis clinic, or its equivalent. Standard differential diagnosis and treatment will not be covered. Particularly stressed will be newer concepts of etiology, newer research techniques and tools, and a detailed summary of recent advances in the basic knowledge of these disorders.

Additional information from: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

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HOME CARE OF SICK CHILDREN

Mothers who must take care of a child with rheumatic fever at home will find much practical help

in a booklet issued by the American Heart Association and its affiliates. Entitled "Home Care of the Child with Rheumatic Fever", the booklet was prepared for parents of youngsters for whom hospital care is either not necessary or not available. It contains basic information and hints useful in the care of sick children generally, and offers practical pointers on home nursing care. Also included are suggestions for dealing with the emotional problems that are likely to arise when a youngster is confined to bed for more than a few days. Copies are available on request to the American Heart Association, Inc., 44 East 23rd St., New York 10, N.Y.

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BRITISH EMPIRE CANCER CAMPAIGN EXCHANGE FELLOWSHIPS

The British Empire Cancer Campaign has established two Fellowships per annum for Canadians. These Fellowships are tenable for twelve months and of an approximate value of £1500 per annum. Travelling expenses of the Fellows from their Canadian residence to England and return will be borne by the National Cancer Institute of Canada. If necessary, an allowance will also be paid for expenses in connection with the work undertaken. The Fellowships are open to those engaged in the clinical and allied sciences and to those working in fundamental research related to cancer.

Application forms may be obtained from: The National Cancer Institute of Canada, 800 Bay Street, Toronto, Ontario.

Applications should be submitted to the above address not later than November 1, 1959. Awards will be announced December 15, 1959. Fellowships will become tenable July 1, 1960.

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AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

The next scheduled examination (Part 1), written, and review of case histories for all candidates will be held in various cities of the United States and Canada and at military centres outside the Continental United States, on Friday, January 15, 1960. Candidates must submit case reports to the office of the Secretary within 30 days of being notified of their eligibility to Part 1.

Current Bulletins may be obtained by writing to: Robert L. Faulkner, M.D., Executive Secretary and Treasurer, 2105 Adelbert Road, Cleveland 6, Ohio.

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A CLINICAL APHORISM IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS

When confronted with relatively slowly progressive neurological disorder involving one limb, with a mild sphincter disturbance and a history suggesting a space occupying lesion of the spinal cord or brain, it may be difficult to resist employing all the accessory investigations such as myelography and air encephalography. In cases of multiple sclerosis, exacerbations of sphincter disturbances after

(Continued on page 80)

Canad. M. A. J.
Sept. 15, 1959, vol. 81

A DOCTOR'S EDUCATION

goes on...and on...and on

"It's not unusual on Heinz, Mrs. Samson"

Another thing you learn . . . mild-flavoured INFANTSOY mixes with special ease to the creamy-smooth texture most babies are found to prefer. It merits your recommendation—for its high protein content, its general nutritional value (added B-Vitamins and iron), and its uniquely acceptable texture and taste. Since INFANTSOY contains no wheat it is indicated where wheat-allergy is a factor.

Samples for tasting or testing — yours for the asking. Write now to HEINZ BABY FOODS, PROFESSIONAL SERVICES DEPT., LEAMINGTON, ONTARIO

Heinz Baby Foods 57

THE GOOD THEY DO NOW—LASTS A LIFETIME

BFM-360

MEDICAL NEWS *in brief*

(Continued from page 77)

myelography have been observed and these accessory investigations carry a certain risk. Ferguson and Liversedge (*Lancet*, 1: 1159, 1959) have noted in the past that signs can outstrip symptoms in multiple sclerosis much more than in any other neurological disorder.

In some 30 cases they have observed a syndrome of frank pyramidal signs in both legs and symptoms in one leg only; in all cases the diagnosis of multiple sclerosis was confirmed by the subsequent course of the disease, and the syndrome is considered of diagnostic value. Two cases are presented to illustrate this syndrome. In the first patient, there was evidence of bilateral pyramidal involvement for many years and from that time she complained only of symptoms in one leg. The second case is presented to emphasize the importance of the absence of symptoms in the other leg as an absolute diagnostic point. In the absence of symptoms, the mere presence of signs does not justify a diagnosis of multiple sclerosis.

MEMORIAL TO WILLIAM BEAUMONT

Medical historians will certainly want a copy of the May 1959 issue of the *Journal of the Michigan State Medical Society*, which is a William Beaumont Memorial Foundation Number. This number starts with a foreword by Whittaker on William Beaumont and his contribution to medicine, while Dr. Beck contributes a note on the building on Mackinac Island started by the doctors of Michigan nine years ago as a memorial to this celebrated army surgeon who conducted experiments on Alexis St. Martin and his gastric fistula. Dr. E. H. Bensley of Montreal contributes a study of Alexis St. Martin (since reproduced in the *Canadian Medical Association Journal* (80: 907, 1959) by kind permission of the editor of the *Journal of the Michigan State Medical Society*). Whittaker has a small contribution on centres of Beaumont interest, as well as an article on some physiologists who preceded Beaumont in studying digestive processes. The issue also contains a bibliography on Beaumont, notes on army uniforms of 1822 and a number of other contributions.

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DISSEMINATED NODULAR PULMONARY OSSIFICATION IN MITRAL STENOSIS

Four new cases of disseminated nodular pulmonary ossification associated with mitral stenosis are described by Wilson, Sasaki and Johnson (*Circulation*, 19: 323, 1959). This rare condition occurs predominantly in young men with mitral stenosis, pulmonary hypertension and congestive heart failure. Radiological examination shows multiple nodular densities throughout the lung fields, due to numerous discrete nodules of bone, measuring 2 to 8 mm. in diameter, and usually located within alveolar sacs or groups of adjacent air spaces.

Detailed lung function studies in one patient with this rare complication of mitral stenosis were normal. Cardiac catheterization findings in this patient and in one other patient with the same disorder showed severe pulmonary hypertension.

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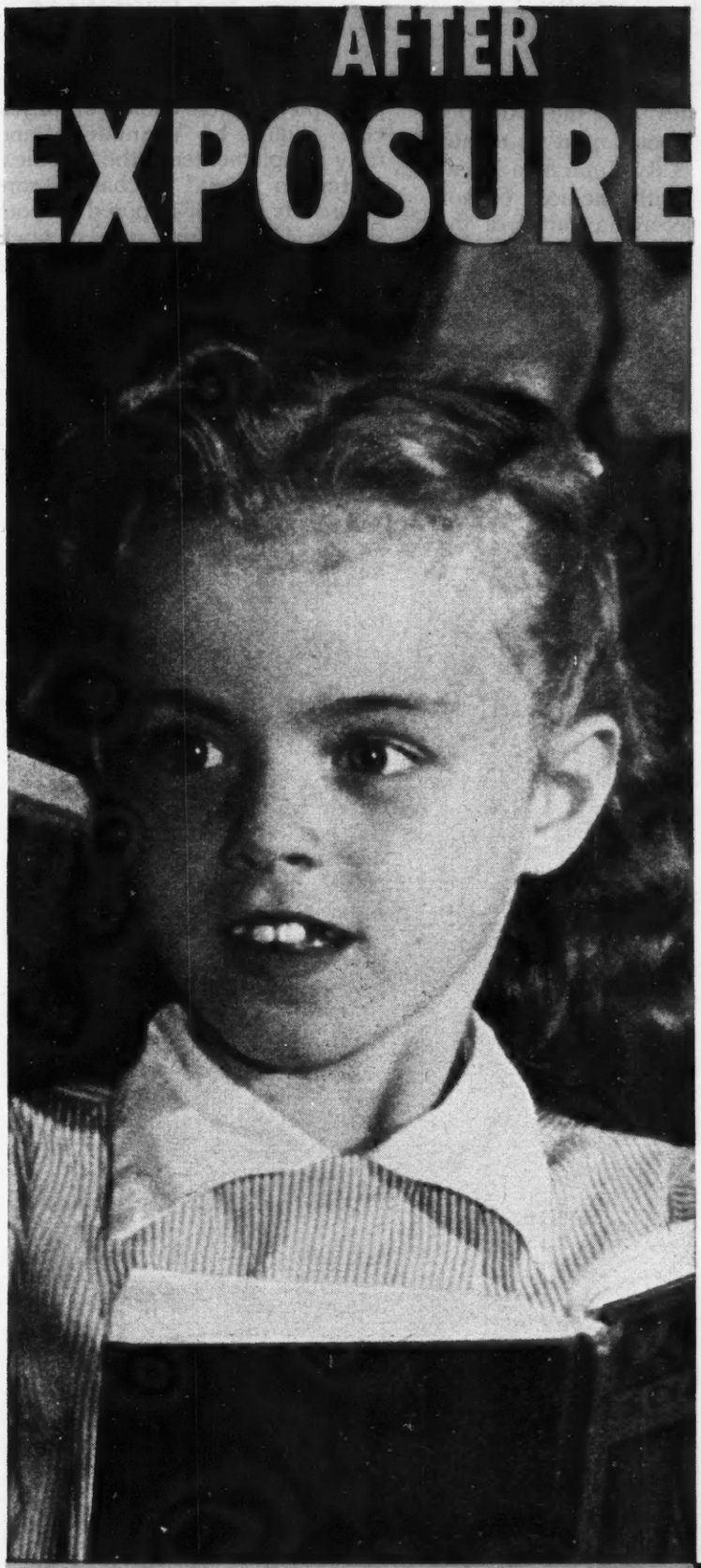

The school child is subject to respiratory tract infection through exposure to cold and wet and contact with playmates with established infection.

FOR THE TREATMENT OF CHILDHOOD INFECTIONS SENSITIVE TO SULFONAMIDES AND PENICILLIN...

- "The low toxicity and bactericidal effect of penicillin, coupled with the bacteriostatic action of sulfonamides, results in a theoretically ideal treatment program."

  Kock, R., and Carson, M. J., Meningococcal Infections in Children, New England J. Med. 258:639, 1958.

- for treatment of pneumococcic, staphylococcic and hemolytic streptococcic infections; in scarlet fever, otitis media, tonsillitis, Vincent's angina and urinary tract infections; and to prevent secondary infection during measles, influenza and whooping cough.

"TRULFACILLIN" BRAND

TRIPLE SULFAS AND PENICILLIN

PEDIATRIC SUSPENSIONS

"TRULFACILLIN" PEDIATRIC 3-200

Each 5 cc. teaspoonful contains:

Sulfamethazine	65 mg.	3 gr.
Sulfadiazine	65 mg.	
Sulfamerazine	65 mg.	
Benzathine penicillin-G	200,000 I.U.	

"TRULFACILLIN" PEDIATRIC 3-100

Each 5 cc. teaspoonful contains:

Sulfamethazine	65 mg.	3 gr.
Sulfadiazine	65 mg.	
Sulfamerazine	65 mg.	
Benzathine penicillin-G	100,000 I.U.	

Dosage: Infants and children — one teaspoonful per day for each 4 pounds of body weight, in divided doses, e.g., child weighing 8 lb. — ½ teaspoonful every six hours; child weighing 16 lb. — 1 teaspoonful every six hours

Bottles of 60 cc.

CAUTION: While untoward effects associated with sulfonamide therapy are greatly reduced by the use of "Trulfacillin" preparations, vigilance should not be relaxed in the search for and recognition of agranulocytosis, fever, joint pains, skin reactions, etc. In rare instances, the injection of penicillin, and more rarely still its oral administration, may cause acute anaphylaxis. The reaction appears to occur more frequently in patients with bronchial asthma and other allergies, or in those who have previously demonstrated sensitivity to penicillin.

PREPARATIONS FOR PEDIATRIC PRACTICE

Charles E. Frosst & Co.

MONTREAL CANADA

MEDICAL NEWS *in brief*

(Continued from page 80)

The pathogenesis of disseminated nodular pulmonary ossification is still unsettled, but the writers agree with the suggestions of others that pulmonary hypertension, interstitial pneumonitis, and congestive heart failure may be the necessary prerequisites for the combination of disseminated nodular pulmonary ossification and mitral stenosis.

AMERICAN MEDICAL ASSOCIATION

Much of the work of the House of Delegates of the American Medical Association at its meeting in Atlantic City, June 8 to 11, was concerned with medical economics. After receiving Part I of their Commission on Medical Care Plans report for information, the delegates adopted a number of recommendations based on this three and a half year study. They agreed that free choice of physician was an important factor in the provision of good medical care, and felt that in order that the principle of free choice of physician should be maintained and fully implemented, the medical profession should discharge more vigorously its self-imposed responsibility for assuring the competency of physicians' services and their provision at a cost which people could afford. The House also recommended that those who receive medical care benefits as a result of collective bargaining should have the widest possible choice from among medical care plans for the provision of such care. The House also stated that each member of the public should be accorded the privilege of selecting and changing his physician at will or selecting his preferred system of medical care.

On the subject of closed-panel plans, the House endorsed the opinion that "there is no generally held opinion declaring that participation in closed-panel medical care plans would render a physician unethical". However, they urged the law division of the A.M.A. to draft a statement which would include all points a physician should consider in contracting with such a plan. The House urged medical profession-sponsored plans to extend their membership and coverage as a deterrent to the development of closed-panel plans, and recommended efforts to improve relationships between occupational health programs and practising physicians.

At their inaugural ceremony, at which Dr. Louis M. Orr of Orlando, Florida, succeeded Dr. Gunnar Gundersen of LaCrosse, Wisconsin, as President of the Association, the guest of honour was President Eisenhower, who called on American physicians to protect the private arrangement between doctor and patient and said that if the time ever came when large numbers of U.S. citizens turned primarily to government for assistance in what ought to remain a private arrangement between doctor and patient, "we shall all have suffered a great loss." The President-Elect was Dr. E. Vincent Askey, a Los Angeles surgeon, who was chosen by a vote of 122 to 81 over Dr. George F. Lull of Chi-

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MEDICAL NEWS *in brief*

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cago, former general manager of the A.M.A.

Relationships with osteopaths were extensively debated. It was recommended that all voluntary professional associations between doctors of medicine and those who practise a system of healing not based on scientific principles be declared unethical. The enactment of medical practice acts requiring all who practise as physicians and surgeons to meet the same qualifications, take the same examinations, and graduate from schools approved by the same agency should be encouraged by constituent associations of the A.M.A. It was not considered unethical for doctors of medicine to teach students in an osteopathic college in the process of being converted into an approved medical school under supervision of the A.M.A. council on medical education and hospitals. It was suggested that a liaison committee be appointed to meet with the representatives of the American Osteopathic Association, if mutually agreeable, to consider problems of common concern including interprofessional relationships on a national level.

The House urged a period of at least two years of formal hospital training after graduation for doctors preparing for family practice. They recommended that the new program include a minimum basic 18-month in-hospital training period to provide broad experience in the pædiatric, diagnostic, therapeutic, psychiatric, preventive and rehabilitation aspects of medicine, together with regularly assigned periods of emergency room service and training in minor surgery and adequate opportunity for study of outpatients. Training in obstetrics should be elective and not mandatory.

The House disapproved of resolutions in favour of compulsory social security coverage for self-employed physicians, but recognizing the apparent growing demand by physicians for economic security they requested an investigation of the possibilities of developing group insurance and retirement plans for A.M.A. members.

NEW OFFICERS FOR T.C.M.P.

At the organization's recent annual meeting in Toronto, Dr. A. H. Lyon of Windsor, Ont., was named chairman of Trans-Canada Medical Plans. Dr. Lyon is a director of Windsor Medical Services. Elected as vice-chairman was Dr. M. R. MacCharles of Winnipeg, a director of Manitoba Health Service. Mr. E. D. Millican of Montreal was re-elected as honorary treasurer and Dr. J. A. Ganshorn of Vancouver as honorary secretary. Dr. Harold Sugarman of Saskatoon was elected a member of the Executive Committee.

OSLER'S "MEN AND BOOKS"

A physician in Pasadena, California, has done the memory of Osler an additional service by having privately printed a collection of all the writings which Osler contributed to the *Canadian Medical Association Journal* under the rubric of Men and Books from 1912 to 1914. In this series, Osler wrote a series of brief sketches,

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mostly biographical, about such persons as William Beaumont, Lænnec, John Shaw Billings and George Bodington, the pioneer of open-air treatment of tuberculosis. Dr. Nation's book, which is simply entitled "Men and Books", has been printed in a limited edition, but inquiries from interested individuals or institutions may be made to the author, whose address is 112 North Madison Avenue, Pasadena 1, California, U.S.A.

COURSE IN AIR POLLUTION

The problems of the sources, effects and control of community air pollution will be treated in an intensive two-week course, "Air Pollution," offered by the New York University Post-Graduate Medical School in co-operation with the N.Y.U. College of Engineering from November 30 to December 11, 1959.

The course, designed for engineers, industrial hygienists and physicians, will review the basic toxicology of the principal air pollutants, micrometeorological factors, effects of air pollution on agriculture and commerce, and methods for sampling and analyzing the various toxic components. Also described will be the nature and methods of control of effluents from power and steam generation, domestic heating, incineration, internal combustion engines, and various industrial processes.

For further information: The Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N.Y.

PHARMACEUTICAL MANUFACTURERS' STATEMENT OF PRINCIPLES

At the spring general meeting, the Canadian Pharmaceutical Manufacturers Association adopted a statement of "Principles of Ethical Drug Promotion," intended as a guide of conduct for members. The statement sets down the position of the members in recognizing their responsibilities and obligations towards not only the medical and pharmaceutical professions but also the lay public. The principles will, it is hoped, be adhered to not only by members of the C.Ph.M.A., but also by pharmaceutical manufacturers who are not members of the Association. The statement is as follows:

"We, members of the Canadian Pharmaceutical Manufacturers Association, recognizing our responsibilities and obligations to promote the public welfare and to maintain honourable relations with the medical and pharmaceutical professions, with associated sciences, and with the public, do pledge ourselves to the following statement of principles:

"1. Prompt, complete, conservative and accurate information concerning medicinal agents shall be made available to the medical and pharmaceutical professions.

"2. Any statement involved in product promotional communications must be supported by adequate and acceptable scientific evidence. Claims must not be stronger than such evidence warrants. Every effort must be made to avoid ambiguity and implied endorsements. Whenever market,

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statistical or background information or references to unpublished literature or observations are used in promotional literature, the source must be available to the physician upon request.

"3. Quotations from medical literature or from personal communications of clinical investigators in promotional communications must not change or distort the true meaning of the author.

"4. If it is necessary to include comparisons of drugs in promotional communications, either written or verbal, such comparisons must be used only when they are constructive to the physician and made on a sound professional and factual basis. Trade marks are private property that can be used legally only by or with the consent of owners of trade marks.

"5. The release to the lay public of information on the clinical use of a new medicinal agent or the new use of an established drug prior to adequate clinical assessment and presentation to the medical profession is not in the best interests of the medical profession or the layman.

"6. All medical claims and assertions contained in promotional communications shall have medical review prior to their release.

"Any violation of these principles brought to the attention of the General Manager of the Canadian Pharmaceutical Manufacturers Association shall be referred by him to the Board of Directors."

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CUMULATIVE INDEX MEDICUS

An old and trusted friend will soon disappear from the scene, for the American Medical Association has decided to discontinue the *Quarterly Cumulative Index Medicus* whose last volumes will include the year 1956, since the index has been lagging behind for a number of years. In its place there will be a joint project of the A.M.A. and the National Library of Medicine, which will begin in 1960. The National Library will index the significant journals and the A.M.A. will publish a cumulative index once a year. It is hoped to publish this index two to three months after the end of a calendar year.

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ANNUAL MEETING, AMERICAN HEART ASSOCIATION

The 1959 Annual Meeting and Scientific Sessions of the American Heart Association will be held in Philadelphia, Pa., from October 23 to October 27. The Scientific Sessions will open on Friday, October 23 and conclude on Sunday, October 25. These sessions, which include six of broad clinical interest, will be held at Philadelphia's Convention Hall.

The A.H.A. Assembly, national delegate body, will meet on Monday and Tuesday, October 26 and 27, at the Bellevue-Stratford Hotel.

Registration and hotel reservation forms are available on request to the American Heart Association, 44 East 23rd St., New York 10, N.Y. Physicians registering in advance for the Scientific Sessions will receive a complimentary copy of the program booklet containing abstracts of the proceedings.

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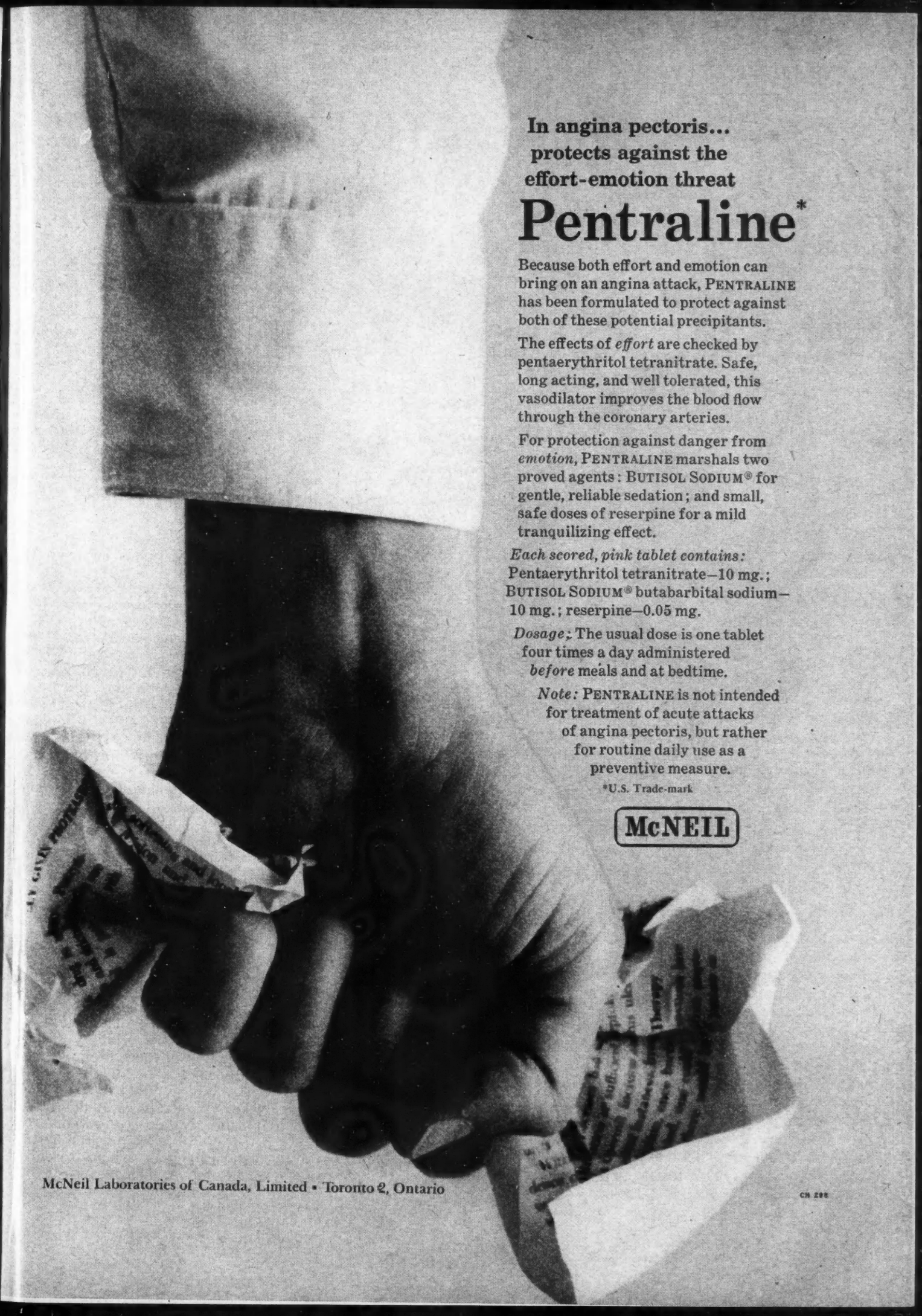

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ALVARENGA PRIZE FOR 1959

On July 14, 1959, the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1959 to Hilary Koprowski, M.D., Professor of Research Medicine, University of Pennsylvania, for his work on the development of a living attenuated virus vaccine against poliomyelitis.

The Alvarenga Prize was established by the will of Pedro Francisco DaCosta Alvarenga of Lisbon, Portugal, an Associate Fellow of the College of Physicians of Philadelphia, to be awarded annually by the College of Physicians on the anniversary of the death of the testator, July 14, 1883.

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PICKER FOUNDATION AWARDS

Four Canadian scientists have been awarded grants for research by the James Picker Foundation. These grants, totalling $16,000, are intended to foster research in radiology in Canada.

The following awards for 1959-60 have been announced by the National Research Council of Canada, which administers the Canadian program of the James Picker Foundation: Dr. R. A. Béique, Department of Radiology, Montreal General Hospital, Montreal—dichromography, a method for quantitative analysis of certain elements using their characteristic absorption edges; Dr. F. Bohatirchuk, Department of Anatomy, University of Ottawa—changes in aging bone as revealed by ultrasoft x-rays; Dr. C. B. Peirce, Radiologist-in-Chief, Royal Victoria Hospital, and Chairman of the Department of Radiology, McGill University, Montreal—incident gonadal dose during medical radiologic procedures; and Dr. R. L. deC. H. Saunders, Chairman of the Department of Anatomy, Dalhousie University, Halifax—microangiography by x-ray projection microscopy.

The U.S. program of the James Picker Foundation is administered by the National Academy of Sciences—National Research Council, Washington, which recently announced additional awards by the Foundation amounting to $70,000.